PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 277/02, 275/02, 307/02, 333/04, A61K 31/00 | A2

(11) International Publication Number: WO 95/00501

(43) International Publication Date: 5 January 1995 (05.01.95)

(21) International Application Number: PCT/CA94/00318

(22) International Filing Date: 9 June 1994 (09.06.94)

(30) Priority Data:
082,196 24 June 1993 (24.06.93) US
179,467 10 January 1994 (10.01.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 179,467 (CIP)
Filed on 10 January 1994 (10.01.94)

(71) Applicant *(for all designated States except US)*: MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DUCHARME, Yves [CA/CA]; 4501 Kensington, Montreal, Quebec H4B 2W6 (CA). GAUTHIER, Jacques, Yves [CA/CA]; Apartment 2, 540 Odette Oligny, Laval, Quebec H7N 5Z4 (CA). PRASIT, Petpiboon [CA/CA]; 177 Argyle Drive, Kirkland, Quebec H9H 5A6 (CA). LEBLANC, Yves [CA/CA]; 8 Lafford, Kirkland, Quebec H9J 3Y3 (CA). WANG, Zhaoyin [CA/CA]; 13199 Edison Crescent, Pierrefonds, Quebec H8Z 1Y5 (CA). LEGER, Serge [CA/CA]; 51 Lamarche, Dollard des Ormeaux, Quebec H9B 3E5 (CA). THERIEN, Michel [CA/CA]; 944 21st Avenue, Laval, Quebec H7R 2R2 (CA).

(74) Agent: MURPHY, Kevin, P.; Swabey, Ogilvy, Renault, Suite 800, 1001 de Maisonneuve Boulevard West, Montreal, Quebec H3A 3C8 (CA).

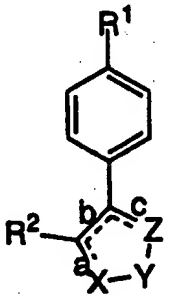
(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHENYL HETEROCYCLES AS CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of formula (I) useful in the treatment of cyclooxygenase-2 mediated diseases. The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of formula (I).



(I)

PHENYL HETEROCYCLES AS CYCLOOXYGENASE-2 INHIBITORS

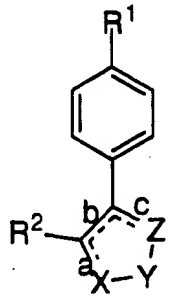
BACKGROUND OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases and methods of treatment thereof.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Up until recently, only one form of cyclooxygenase had been characterized, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. Recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has now also been cloned, sequenced and characterized from sheep, murine and human sources. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug,

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I useful in the treatment of cyclooxygenase-2 mediated diseases



I

or pharmaceutically acceptable salts thereof wherein:

X–Y–Z–is selected from the group consisting of:

(a) -$CH_2CH_2CH_2$-,
(b) -$C(O)CH_2CH_2$-,
(c) -$CH_2CH_2C(O)$-,
(d) -$CR^5(R^{5'})$-O-C(O)-,
(e) -C(O)-O-$CR^5(R^{5'})$-,
(f) -CH_2-NR^3-CH_2-,
(g) -$CR^5(R^{5'})$-NR^3-C(O)-,
(h) -CR^4=$CR^{4'}$-S-,
(i) -S-CR^4=$CR^{4'}$-,
(j) -S-N=CH-,
(k) -CH=N-S-,
(l) -N=CR^4-O-,
(m) -O-CR4=N-
(n) -N=CR^4-NH-;
(o) -N=CR^4-S-, and
(p) -S-CR^4=N-;
(q) -C(O)-NR^3-$CR^5(R^{5'})$-;

(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, including fluoro, chloro, bromo and iodo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$, and
(10) $-C(R^5)(R^6)-O-C_{1-4}$alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^3 is selected from the group consisting of
(a) hydrogen,
(b) CF_3,

R^5, $R^{5'}$, R^6, R^7 and R^8 are each independently selected from the group consisting of

(a) hydrogen,

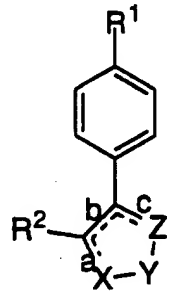
(b) C_{1-6}alkyl,

or R^5 and R^6 or R^7 and R^8 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q is CO_2H, CO_2-C_{1-4}alkyl, tetrazolyl-5-yl, $C(R^7)(R^8)(OH)$, or $C(R^7)(R^8)(O\text{-}C_{1-4}alkyl)$;

provided that when X-Y-Z is -S-CR^4= $CR^{4'}$, then R^4 and $R^{4'}$ are other than CF_3 .

In one aspect, within this embodiment are the compounds of formula I



I

or pharmacetically acceptable salts thereof wherein:

X-Y-Z- is selected from the group consisting of -C(O)-O-$CR^5(R^{5'})$- when side b is a double bond, and sides a and c are single bonds; and

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(e) -C(O)-O-$CR^5(R^{5'})$-,
(f) -CH_2-NR^3-CH_2-,
(g) -$CR^5(R^{5'})$-NR^3-C(O)-,
(h) -CR^4=$CR^{4'}$-S-,
(i) -S-CR^4=$CR^{4'}$-,
(j) -S-N=CH-,
(k) -CH=N-S-,
(l) -N=CR^4-O-,
(m) -O-CR4=N-
(n) -N-CR^4-NH-,
(o) -N=CR^4-S-, and
(p) -S-CR^4=N-,
(q) -C(O)-NR^3-$CR^5(R^{5'})$-;
(r) -NR^3-CH=CH- provided R^1 is other than -$S(O)_2$Me,
(s) -CH=CH-NR^3- provided R^1 is other than -$S(O)_2$Me.

Within this genus is the sub-genus of compounds of formula I wherein

R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)NHCH_3$,
(e) $S(O)NHNH_2$, and
(f) $S(O)NHNHC(O)CF_3$;

R^2 is selected from the group consisting of
(a) C_{1-4}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
(1) hydrogen,
(2) fluoro, chloro, and bromo,

(5) CF_3,
(6) C_{1-4}alkyl,
(7) N_3,
(8) $-C(R^5)(R^6)$-OH,
(9) $-C(R^5)(R^6)$-O-C_{1-4}alkyl.

Within this sub-genus is the class of compounds of formula I wherein

R^2 is selected from the group consisting of
(a) cyclohexyl, and
(b) mono- or di-substituted phenyl, and
wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-4}alkyl,
(8) N_3, and
(9) $-C(R^5)(R^6)$-OH;

R^3 is selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) C_{1-3}alkyl and hydroxyC_{1-3}alkyl,
(d) CN,

R^4 and $R^{4'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) C_{1-3}alkyl,
(d) CN,

Within this sub-class is the group of compounds of formula I wherein

X–Y–Z–is selected from the group consisting of:

(a) -CH_2-O-C(O)-, and

(b) -C(O)-O-CH_2-, and

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)NHCH_3$, and

(d) $S(O)NHNH_2$;

R^2 is

mono or di-substituted phenyl wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo,

(3) methoxy, and

(4) methyl.

This group may be more particularly defined as the compounds of formula I wherein

X–Y–Z–is selected from the group consisting of:

(a) -CH_2-O-C(O)-, and

(b) -C(O)-O-CH_2-, and

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and

(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substitutents are selected from the group consisting of

(1) hydrogen,

Within this class there is the sub-class of compounds of formula I wherein

R^2 is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) 2-furanyl,
(2) 3-furanyl,
(3) 2-thienyl,
(4) 3-thienyl,
(5) 3-isoxazolyl,
(6) 4-isoxazolyl,
(7) 5-isoxazolyl,
(8) 3-isothiazolyl,
(9) 4-isothiazolyl,
(10) 5-isothiazolyl,
(11) 2-oxazolyl,
(12) 4-oxazolyl,
(13) 5-oxazolyl,
(14) 2-thiazolyl,
(15) 4-thiazolyl,
(16) 5-thiazolyl,
(17) 1,2,3-thiadiazol-4-yl,
(18) 1,2,3-thiadiazol-5-yl,
(19) 1,2,4-thiadiazol-3-yl,
(20) 1,2,4-thiadiazol-5-yl,
(21) 1,3,4-thiadiazol-2-yl,
(22) 1,2,5-thiadiazol-3-yl,
(23) 1,2,3-oxadiazol-4-yl,
(24) 1,2,3-oxadiazol-5-yl,
(25) 1,2,4-oxadiazol-3-yl,
(26) 1,2,4-oxadiazol-5-yl,
(27) 1,3,4-oxadiazol-2-yl,

(16) 1,2,4-thiadiazol-5-yl,
(17) 1,3,4-thiadiazol-2-yl,
(18) 1,2,5-thiadiazol-3-yl,
(19) 1,2,3-oxadiazol-4-yl,
(20) 1,2,3-oxadiazol-5-yl,
(21) 1,2,4-oxadiazol-3-yl,
(22) 1,2,4-oxadiazol-5-yl,
(23) 1,3,4-oxadiazol-2-yl,
(24) 1,2,5-oxadiazol-3-yl,
(25) 1,2-diazinyl,
(26) 1,3-diazinyl, and
(27) 1,4-diazinyl.

These heteroaryls may be more particularly defined as being selected from the group consisting of
(1) 3-isothiazolyl,
(2) 4-isothiazolyl,
(3) 5-isothiazolyl,
(4) 2-oxazolyl,
(5) 4-oxazolyl,
(6) 5-oxazolyl,
(7) 2-thiazolyl,
(8) 4-thiazolyl,
(9) 5-thiazolyl,
(10) 1,2-diazinyl,
(11) 1,3-diazinyl, and
(12) 1,4-diazinyl, and

wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) fluoro or chloro,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,

(e) =N-O-CH=,
(f) =CH-O-N=,
(g) =N-S-N=,
(h) =N-O-N=.

Within this genus is the sub-genus of compounds of formula I wherein

R^1 is selected from the group consisting of
- (a) $S(O)_2CH_3$,
- (b) $S(O)_2NH_2$,
- (c) $S(O)_2NHC(O)CF_3$,
- (d) $S(O)(NH)CH_3$,
- (e) $S(O)(NH)NH_2$, and
- (f) $S(O)(NH)NHC(O)CF_3$;

R^2 is selected from the group consisting of
- (a) C_{1-4}alkyl,
- (b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
- (c) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
  - (1) hydrogen,
  - (2) fluoro, chloro, and bromo,
  - (3) C_{1-4}alkoxy,
  - (4) C_{1-4}alkylthio,
  - (5) CN,
  - (6) CF_3,
  - (7) C_{1-4}alkyl,
  - (8) N_3,
  - (9) $-CO_2H$,
  - (10) $-CO_2-C_{1-3}$alkyl,
  - (10) $-C(R^5)(R^6)-OH$, and
  - (11) $-C(R^5)(R^6)-O-C_{1-3}$alkyl,

Within this sub-genus there is the class of compounds of formula I wherein

R^2 is selected from the group consisting of

(a) cyclohexyl, and

(b) mono or di substituted phenyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-4}alkoxy,

(4) C_{1-4}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-4}alkyl,

(8) N_3, and

(9) $-C(R^5)(R^6)-OH$;

R^3 is selected from the group consisting of

(a) hydrogen,

(b) CF_3,

(c) C_{1-3}alkyl and hydroxyC_{1-3}alkyl,

(d) CN;

R^5, $R^{5'}$, R^6, are each independently selected from the group consisting of

(a) hydrogen,

(b) methyl or ethyl,

or R^5 and R^6 together with the carbon to which they are attached form a saturated carbon ring of 4, 5 or 6 atoms.

Within this class there is the sub-class of compounds of formula I wherein

X–Y–Z–is selected from the group consisting of:

(a) =CH-O-CH=,

(b) =N-S-N=,

intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -$SCH_2CH_2CH_3$.

Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like.

Benzoheteroaryl includes the above heteroaryl rings to which it is possible to fuse a benzene ring.

Exemplifying the invention are:

(a) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene,

(b) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,

(c) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene,

(d) 3-(4-(Aminosulfonyl)phenyl)-2-cyclohexylthiophene,

(e) 5-(4-Carboxyphenyl)-4-(4-(methylsulfonyl)phenyl)thiophene-2-carboxylic acid,

(f) 4-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)thiazole,

(g) 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

(h) 4-(4-(Methylsulfonyl)phenyl)-5-(4-fluorophenyl)-isothiazole,

(i) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(j) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*5H*)-furanone,

(k) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan,

(b) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or a pharmaceutically acceptable salt thereof.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

For purposes of this specification a compound is said to selectively inhibit COX-2 in preference to COX-1 if the ratio of the IC50 concentration for COX-1 inhibition to COX-2 inhibition is 100 or greater.

neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compounds of formula I may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease (ie Alzheimer's dementia).

Compounds of formula I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor and asthma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems (including those relating to reduced or impaired platelet function); kidney disease (eg impaired renal function); those prior to surgery or taking anticoagulants; and those susceptable to NSAID induced asthma.

Similarly, compounds of formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine,

or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid

and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-

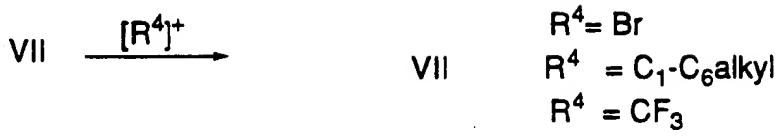
The compounds of the present invention can be prepared according to the following methods.

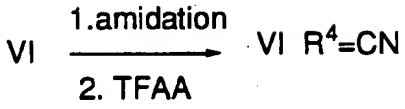
Method A:

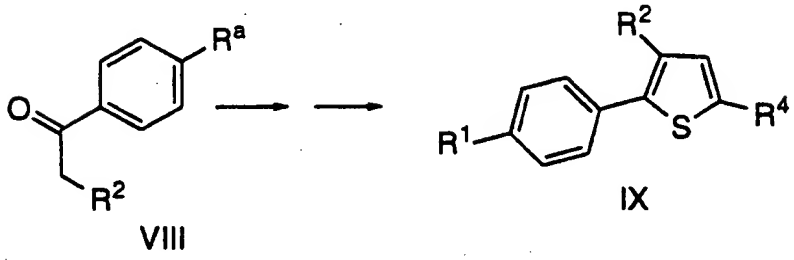
The β-chlorovinylaldehyde III can be obtained from the ketone II and the Vilsmeier reagent (DMF-$POCl_3$) using the general method described by Weissenfels (Z. Chem. 1966, 6, 471). The thiophene compound IV is obtained from III using the general method described by Weissenfels (Z. Chem., 1973, 13, 57). The thiol compound V can be obtained after oxidation of compound IV (R^a = -SMe) with one equivalent of m-CPBA followed by treatment of the resulting sulfoxide with TFAA at reflux. The sulfonamide group (VI) can then be formed by the method of Kharash (J. Amer. Chem. Soc. 1951, 73, 3240). The hydrolysis of compound VI and decarboxylation with Cu bronze in quinoline provides compound VII. Compound VII (R^4 = H) can be treated with halogenating agent such as bromine in acetic acid to allow the preparation of the 5-bromothiophene (VII, R^4 = Br). When it is desired to have a nitrile group at C-5, this can be accomplished from VI via amide formation using the Weinreb methodology (Tetrahedron Letters, 1977, 4171) followed by dehydration with TFAA. The CF_3 group can be introduced at C-5 of VII via the method of Girard (J. Org. Chem. 1983, 48, 3220).

The introduction of an alkyl group at C-5 can be achieved via a Friedel-Crafts reaction on VII (R^4 = H) and an acyl chloride, Cl-CO-lower alkyl and a catalyst such as $TiCl_4$, followed by reduction. For R^4=Me, this can be achieved from the ester (R^4=CO_2Me) via a DIBAL-H reduction followed by deoxygenation using the method of Lau (J. Org. Chem. 1986, 51, 3038). Tertiary alcohols (R^4= - $C(CH_3)_2OH$) can be obtained from VI and MeMgBr. These tertiary alcohols can also be deoxygenated using the method of Lau. Similarly, the thiophene IX can be prepared from ketone VIII.

METHOD A CONT'D



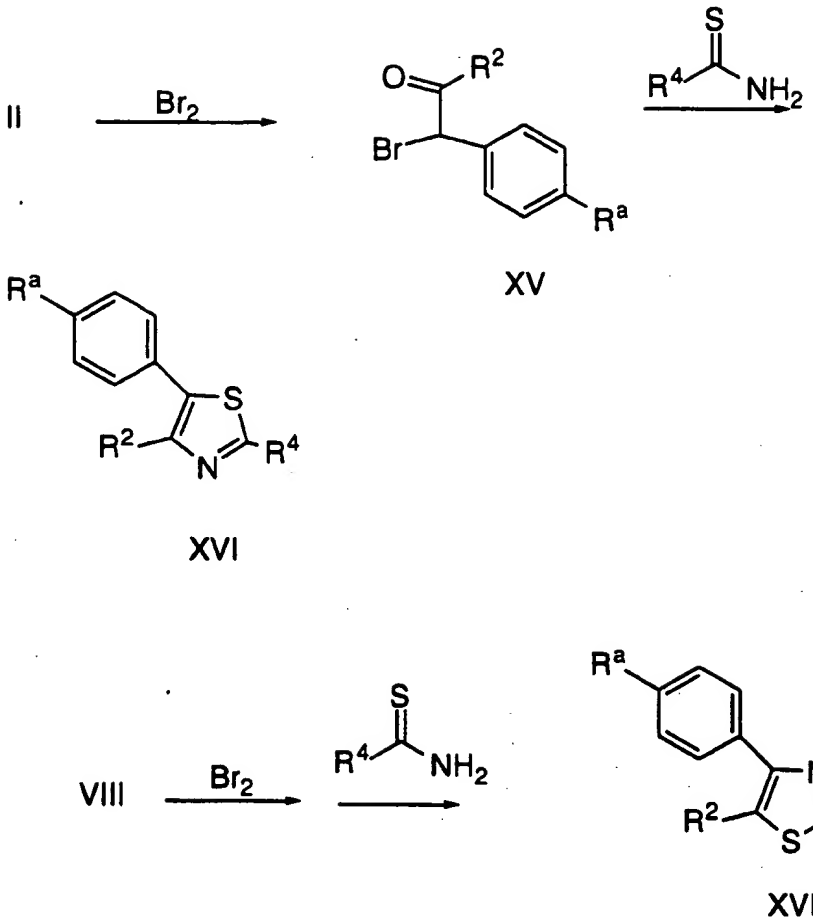




Method B:

Ketone X can be converted to the thiophene compound XI using general methods already described in Method A. The thiophene XII can be prepared by metallation of XI with n-BuLi, quenching with methyl phosphonic dichloride and addition of water or ammonia (X' = OH or NH_2). Similarly, the other regioisomer XIV can be prepared from ketone XIII.

METHOD C



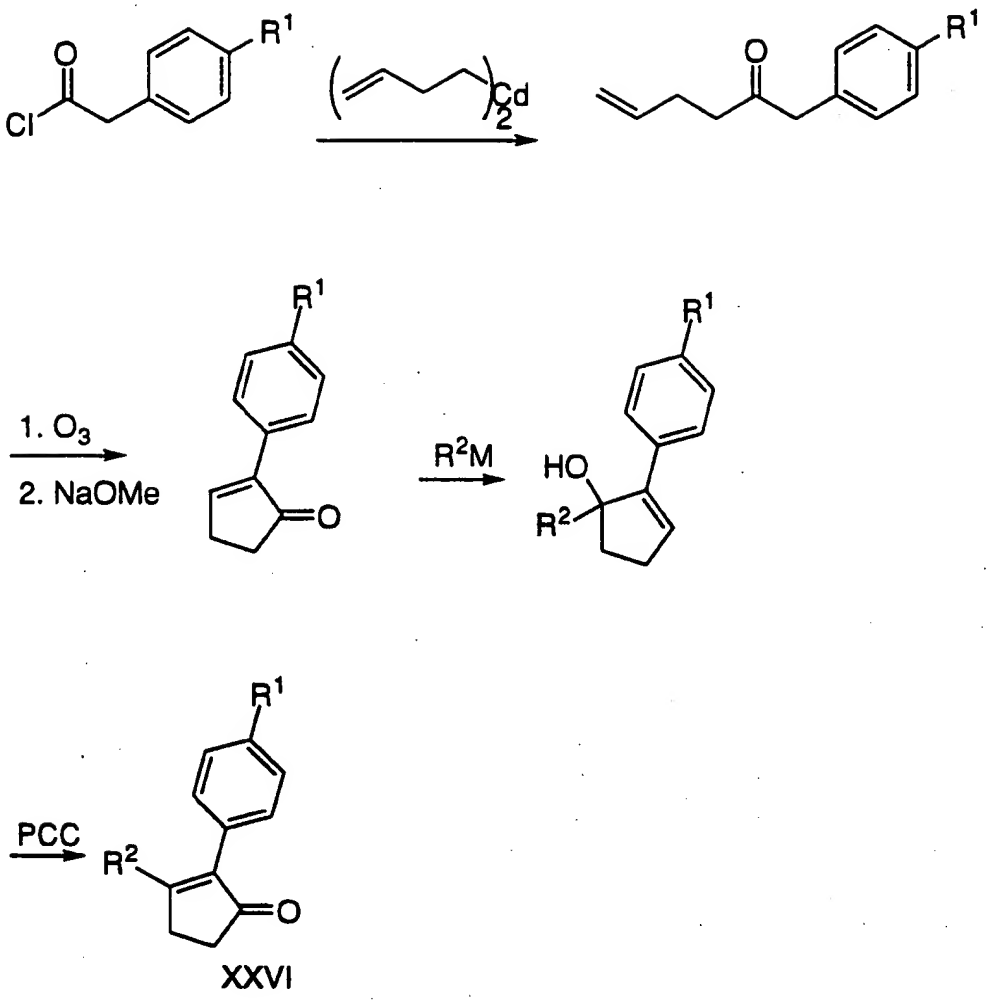
Method D:

Ketone XV can be converted to the imidazole compound XVIII after treatment with formamide using the preparation of Brederick et al, Chem. Ber. 1953, p. 88.

Method F:

The compounds of type XXV can be prepared from readily available 4-substituted phenylacetyl chlorides XXIa. Reaction of di(3-butenyl)cadmium with a 4-substituted phenylacetyl chloride provides ketone XXI. Ozonolysis of XXI affords keto aldehyde XXIb which is cyclized by base to give cyclopentenone XXII. Addition of arylmagnesium bromide or aryllithium to XXII gives allylic alcohol XXIV. Oxidation of XXIV with pyridinium chlorochromate affords the desired 2,3-disubstituted cyclopentenone XXV. For preparation of compound XXV (R^1=SO_2Me), 4-methylthiophenyllithium is used followed by oxidation with the magesium salt of monoperoxyphthalic acid (MMPP) or m-chloroperoxybenzoic acid (mCPBA) to introduce the required methylsulfonyl group in XXV.

METHOD G



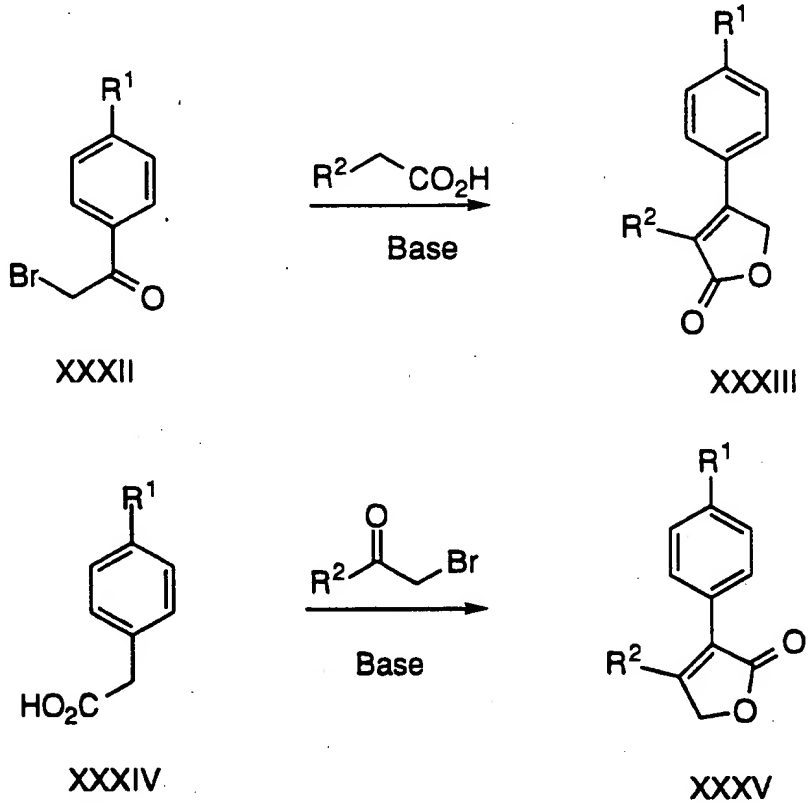
XXVI

Method H:

The 4,5-disubstituted isothiazoles and isothiazol-3(2H)-one-1,1-dioxides can be prepared by the general method described by B. Schulze et al, Helvetica Chimica Acta, 1991, 74, 1059. Thus, aldehyde III (R^a=SO_2Me) or XXVII is treated with excess NH_4SCN in refluxing acetone to provide the corresponding 4,5-disubstituted isothiazoles XXX

as acetonitrile in the presence of a base such as triethylamine and then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford either the lactone XXXIII or XXXV.

METHOD I



XXXII XXXIII

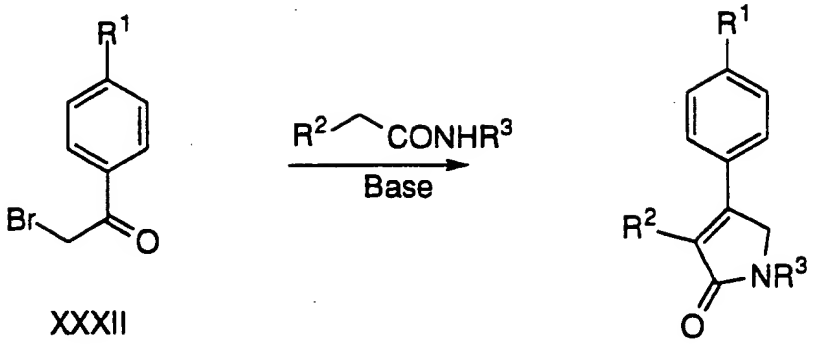
XXXIV XXXV

(R^2 is a mono- or disubstituted phenyl or a mono- or disubstituted heteroaryl)

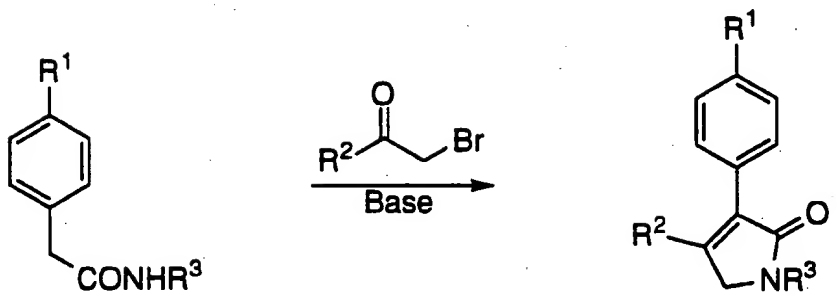
Method J:

Either of the lactones XXXIII or XXXV in a solvent such as THF is reacted with a reducing agent such as diisobutyl aluminium hydride or lithium borohydride at -78°C, to yield the furan XXXVI.

METHOD K



XXXII XXXVII

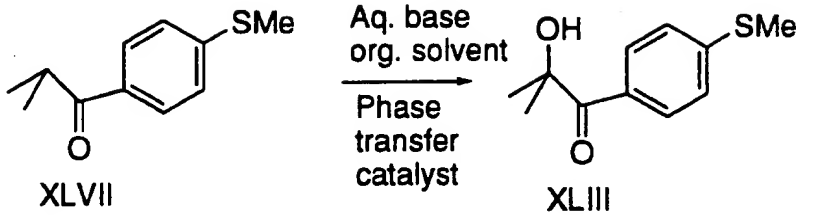


XXXVIII XXXIX

Method L:

Methyl 2-hydroxy isobutyrate is silylated with TMSCl to give the TMS ether XLI, which is treated with 4-methylthiophenyllithium to provide ketone XLII. Desilylation followed by acylation yields keto-ester XLIV, which can be cyclized to lactone XLV by base catalysis. Oxidation of XLV with MMPP or mCPBA affords the desired product XLVI.

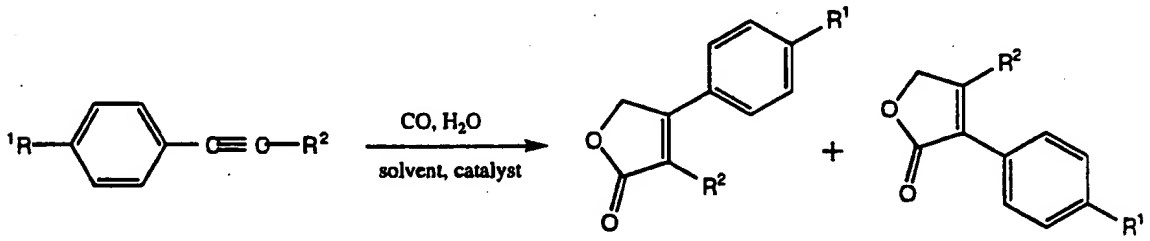
METHOD M



XLVII XLIII

An alternative preparation of the hydroxy ketone XLIII is the oxidation of the known (J. Org. Chem. 1991 56, 5955-8; Sulfur Lett. 1991, 12, 123-32) ketone XLVII. A mixture of XLVII, aqueous base, such as NaOH, organic solvents such as carbon tetrachloride/toluene and a phase transfer catalyst such as ALIQUAT 336 is stirred in air at room temperature to provide XLIII. Compound XLIII is also described in U.S. 4,321,118 and Org. Coat. 1986, 6, 175-95.

Method N

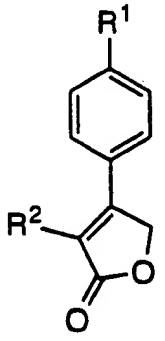


XLVIII XXXIII XXXV

By reacting an acetylene XLVIII with carbon monoxide and water in the presence of suitable catalysts, a mixture of compound XXXIII and its isomer XXXV is obtained. The isomers are separable by standard procedures in the art such as chromatography or crystallization. Examples of useful catalysts and conditions are $PdCl_2$ in aqueous HCl and EtOH,

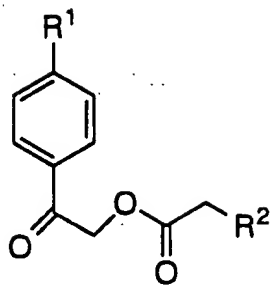
and $Cu(OAc)_2$ and O_2 in MeOH or by the method of Magnus using $PhIO/TMSN_3$ and Bu_4NF. Introduction of the iodine can be accomplished by treating LII with I_2 in the presence of pyridine to afford LIII. Palladium catalyzed Susuki or Stille coupling of LIII with the appropriate aryl or alkyl partner such as the boronic acid LIV provides the butenolide LV. The sulfide can be oxidized to a sulfone by various oxidizing agents such as peracetic acid, MPPM, MMPP or H_2O_2 to give the desired compound LVI. See Y. Ito et. al., *J. Am. Chem. Soc.* **1979**,*101*, 494; and P. Magnus et. al., *Tet. Lett.* **1992**, 2933.

Accordingly, in a further aspect the invention is directed to a process of making a compound of formula XXXIII



XXXIII

comprising:

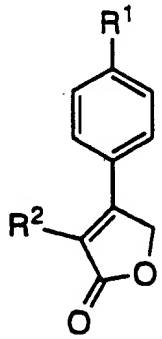


A

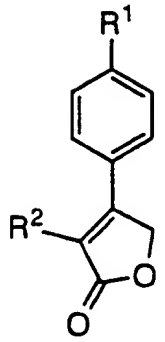
(a3) treating in a non-aqueous polar solvent a compound of formula A with strong base to yield a compound of formula XXXIII.

For purposes of this specification the non-aqueous polar solvent shall be defined to include, but not be limited to, acetonitrile propionitrile, acetone, 2-butanone and tetrahydrofuran. Similarly, the base is defined to include, but not be limited to a tri-C_{1-3}alkylamine such as tri-ethylamine. Moreover, the strong base is defined to include, but not be limited to, an amidine, a guanidine, lithium diisopropylamide and potassium bis-(trimethylsilyl) amide.

In an alternative, the invention is directed to a process of making a compound of formula XXXIII



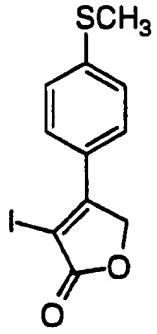
XXXIII



XXXIII

comprising:

(c1) reacting a compound of formula LIII



LIII

with a reagent of the formula $(HO)_2BR^2$ in an aqueous solvent such as benzene, toluene, THF, MeOH, DME or EtOH and in the presence of a suitable palladium catalyst to yield a compound of formula LV, and

Table I

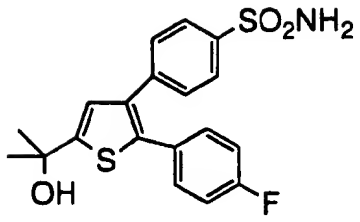
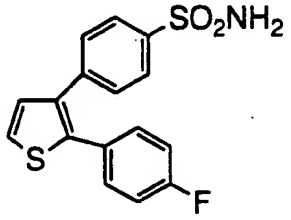
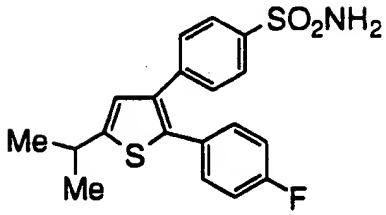
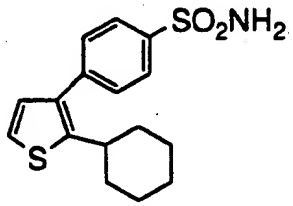
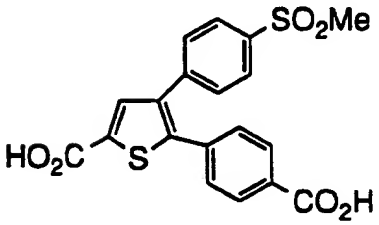
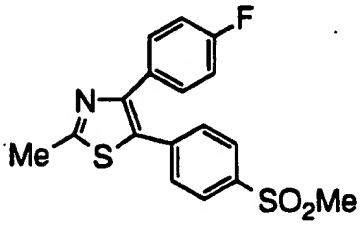
	Example	Method
	1	A
	2	A
	3	A
	4	A
	5	A
	6	C

Table I (continued)

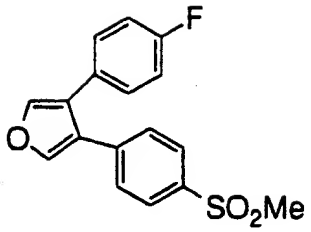
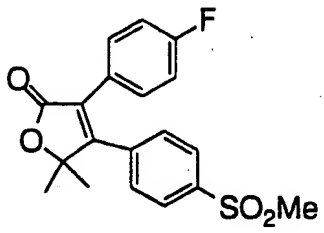
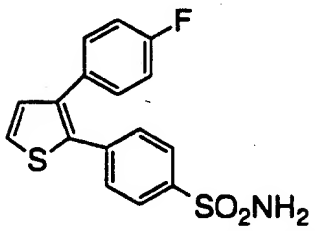
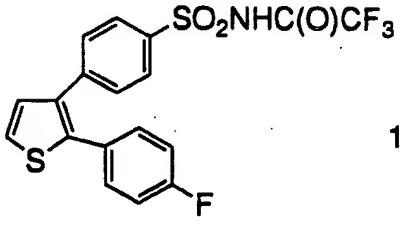
Example	Method
	11 J
	12 L
	13 A
	14 A

Table I (continued)

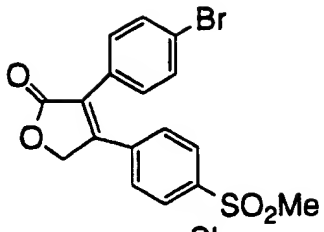
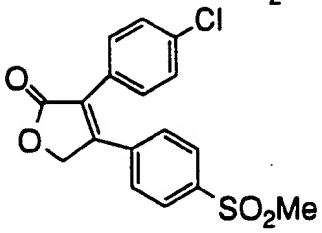
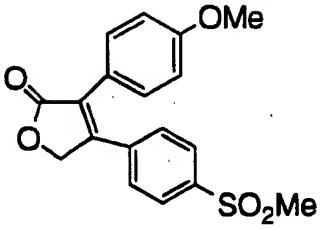
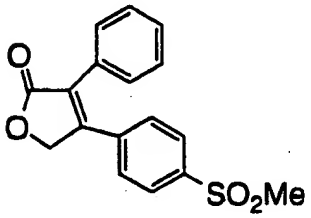
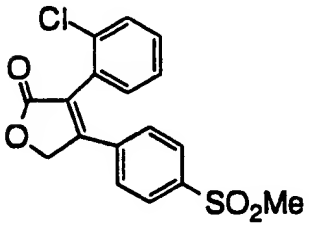
		Example	Method
5		20	I
10		21	I
15		22	I
20		23	I
25		24	I
30			

Table I (continued)

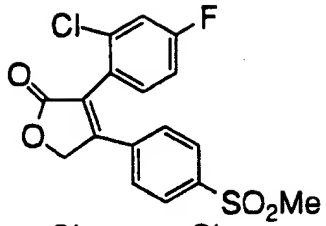
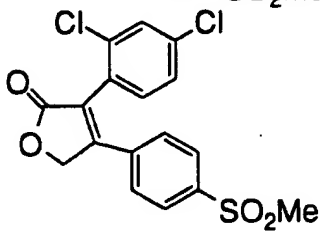
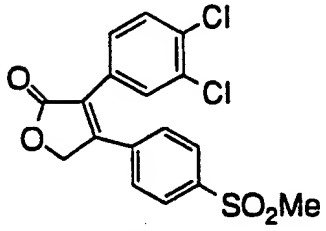
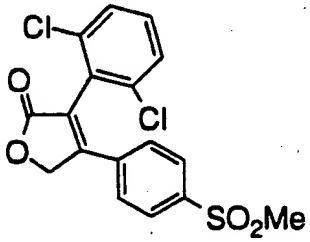
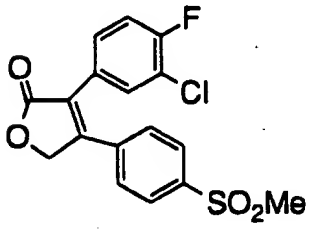
		Example	Method
5		30	I
10		31	I
15		32	I
20		33	I
25		34	I
30			

Table I (continued)

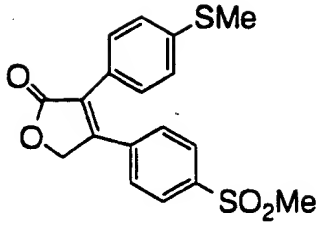
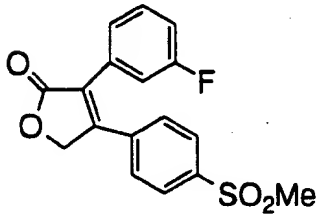
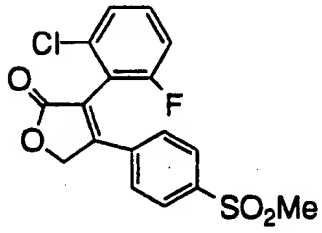
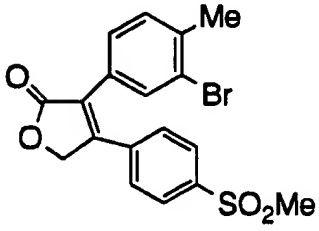
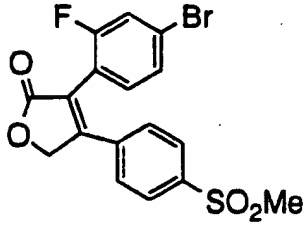
		Example	Method
5		40	I
10		41	I
15		42	I
20		43	I
25		44	I
30			

Table I (continued)

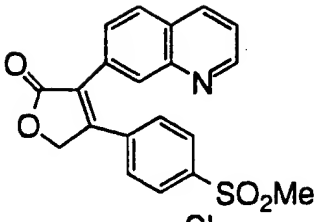
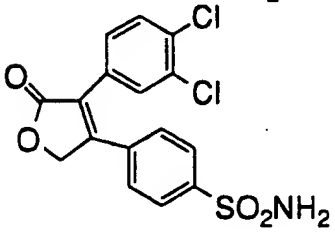
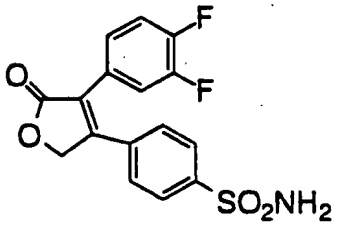
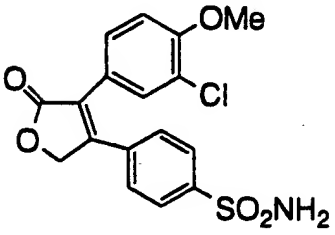
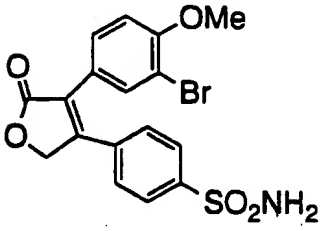
		Example	Method
5		50	I
10		51	I
15		52	I
20		53	I
25		54	I
30			

Table I (continued)

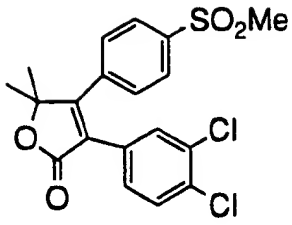
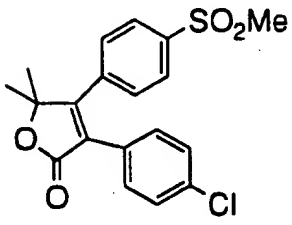
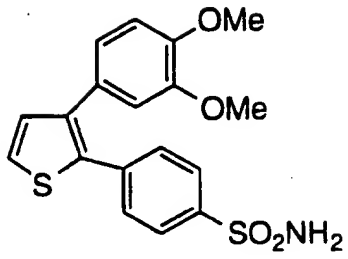
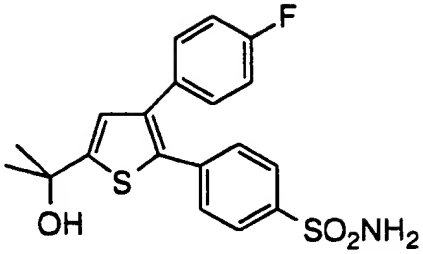
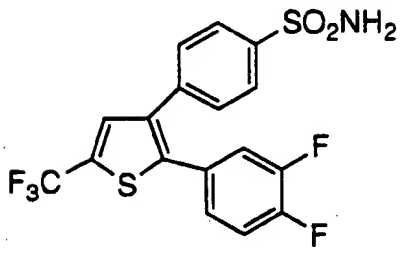
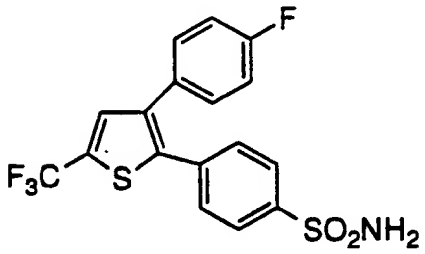
	Example	Method
	59	L + M
	60	L + M

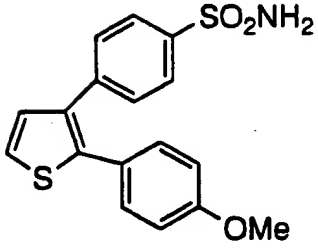
Table II (continued)











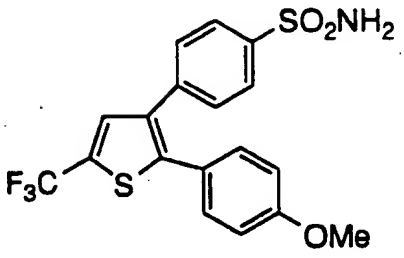
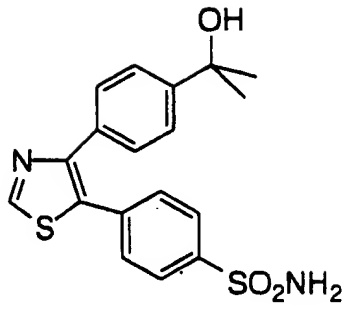
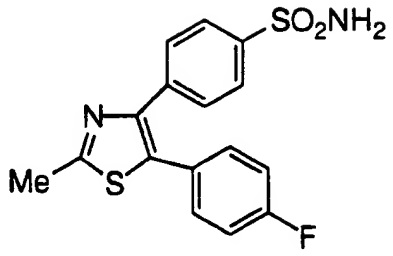
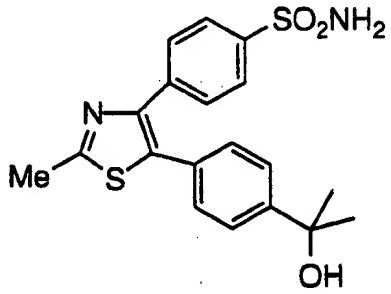
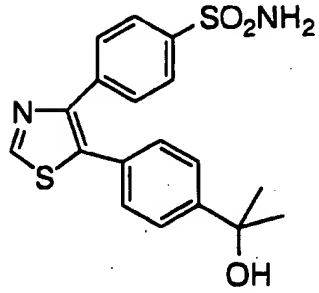


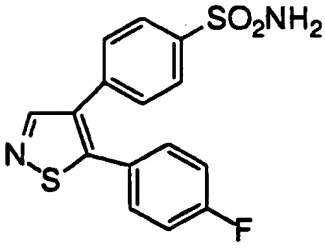
Table II (continued)











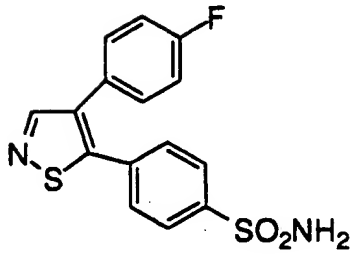
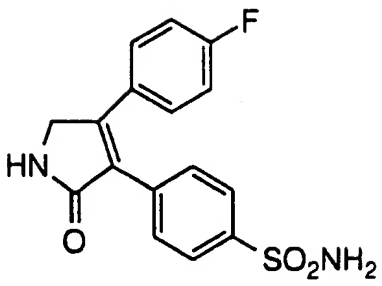
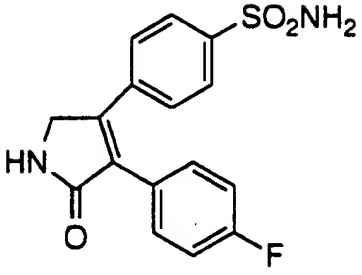
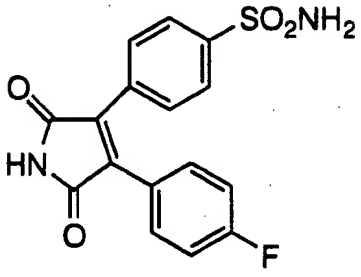
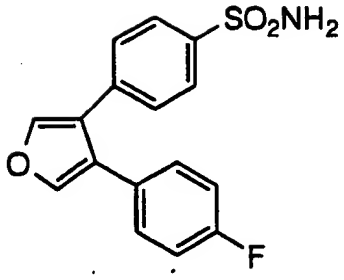


Table II (continued)









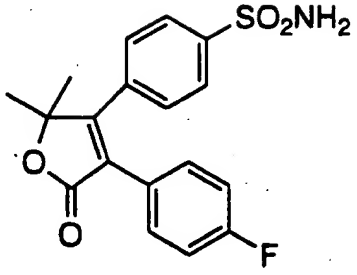
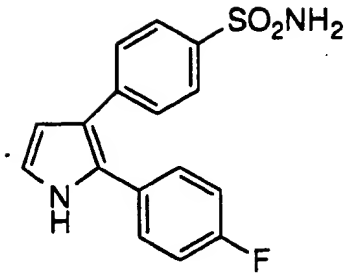
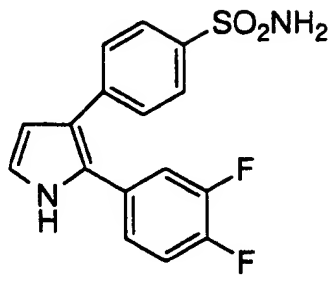
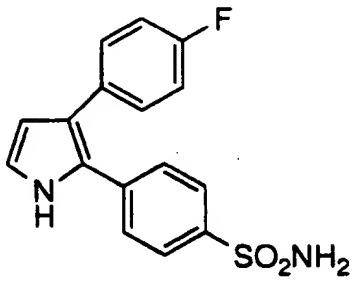
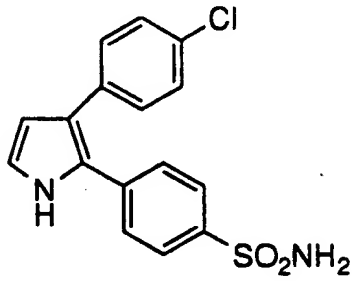


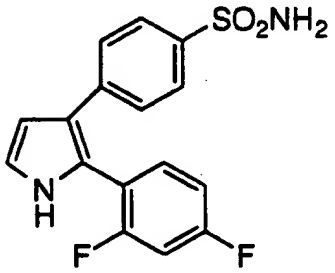
Table II (continued)

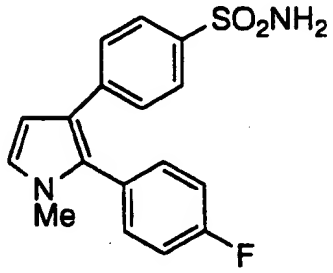


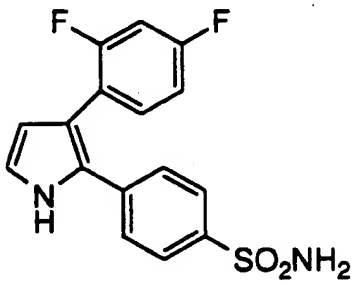












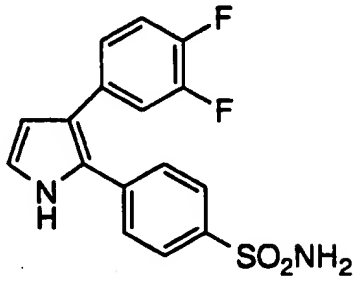


Table II (concluded)

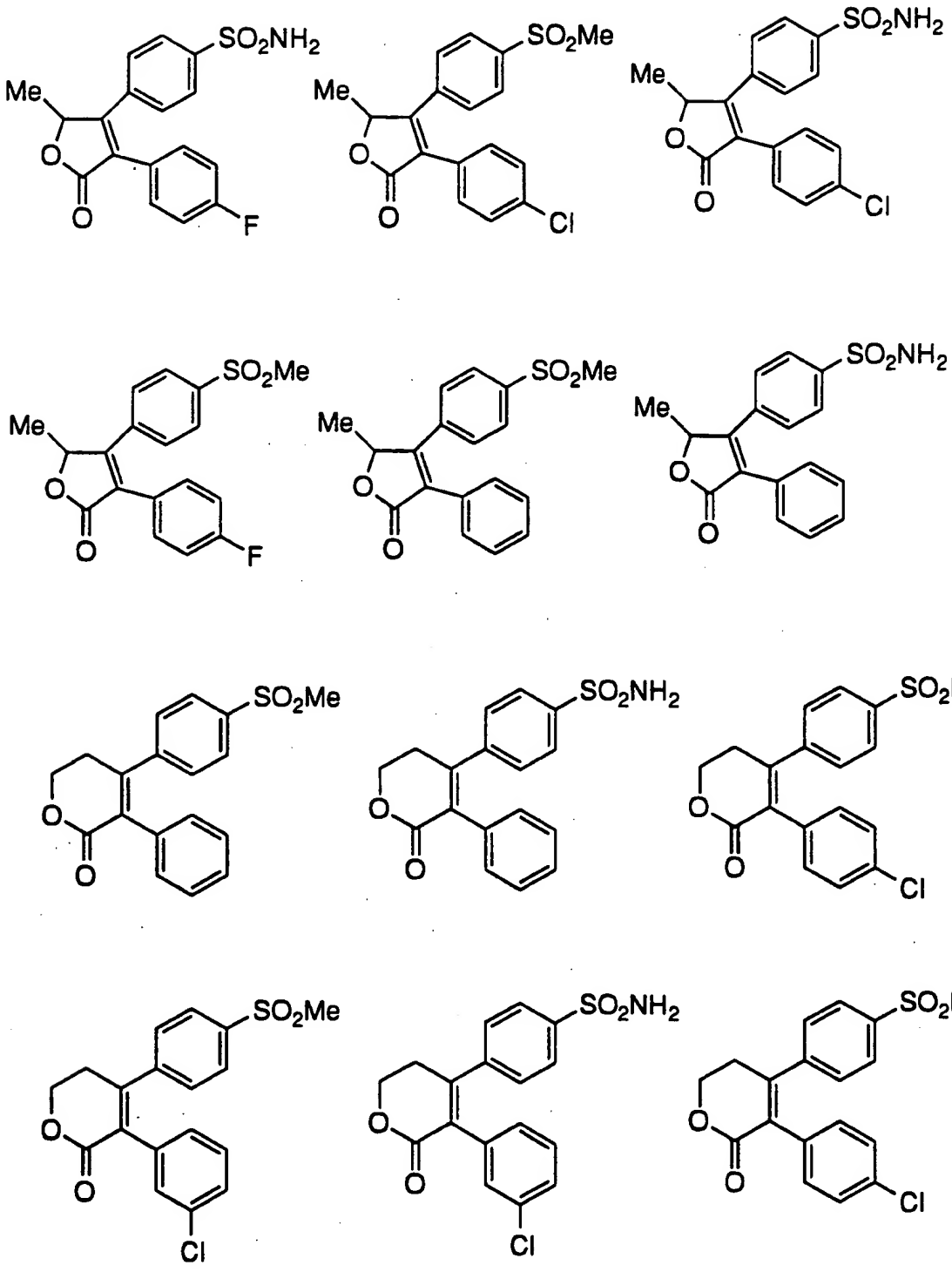
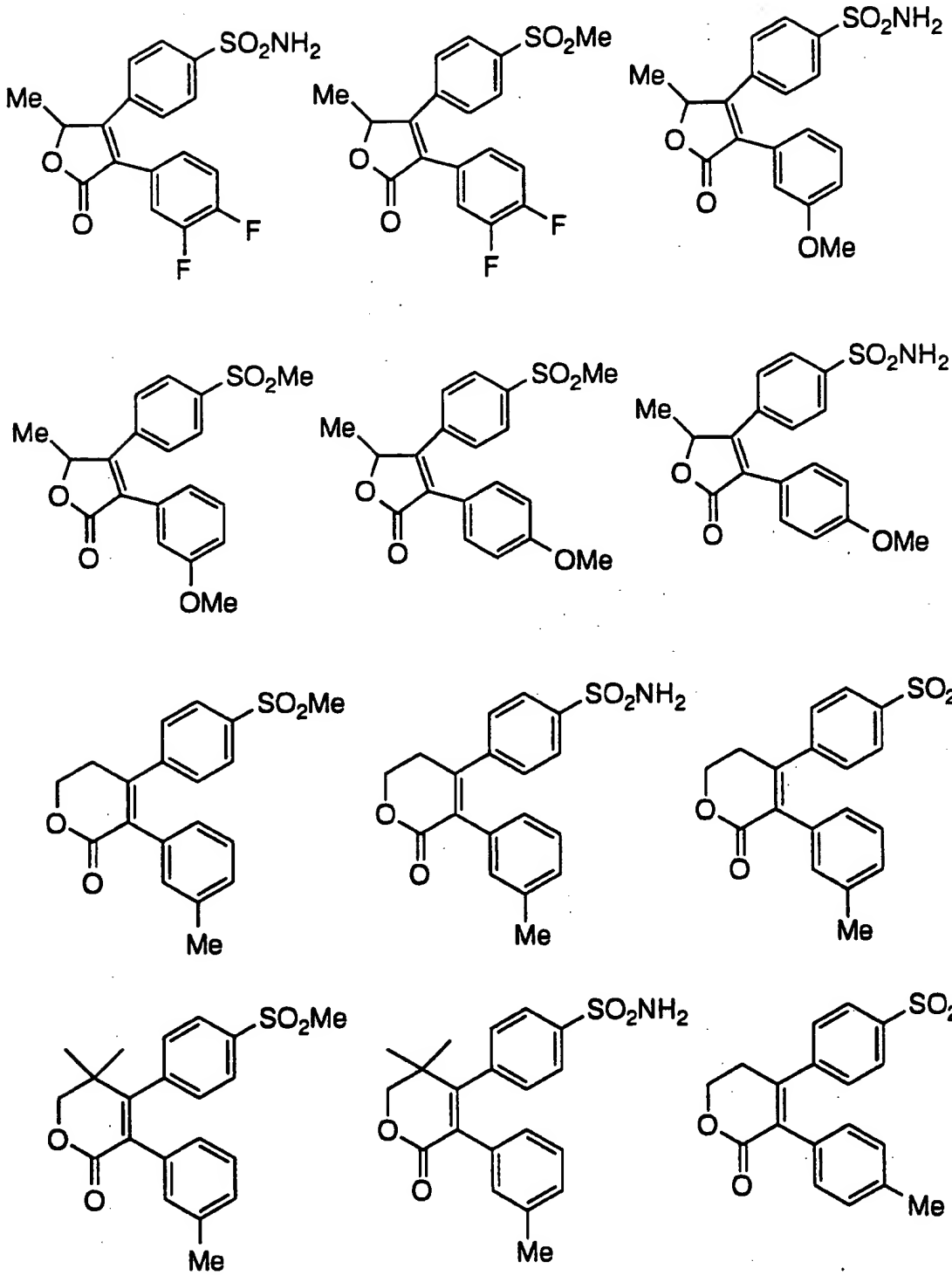


Table II (concluded)

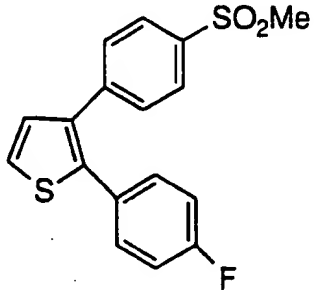
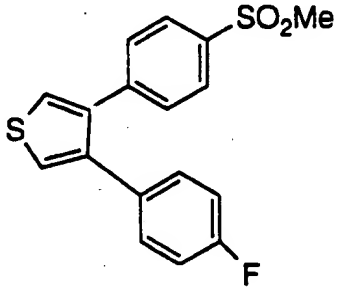


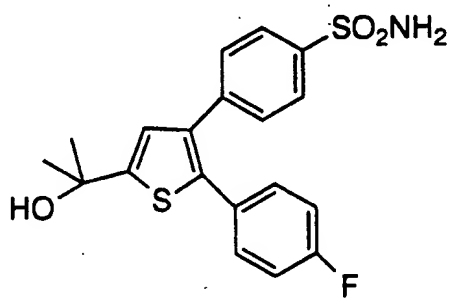
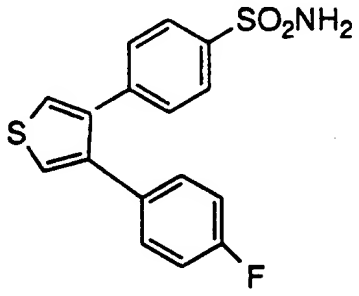
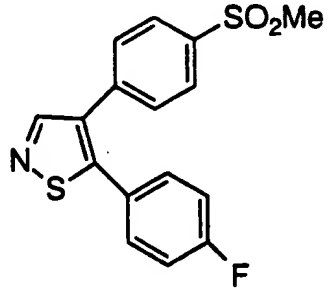
increases in paw volume (V_{3h} - V_{Oh}) were calculated. The animals were euthanized by CO_2 aphyxiation and the absence or presence of stomach lesions scored. Stomach scores were expressed as the sum of total lesions in mm. Paw edema data were compared with the vehicle-control group and percent inhibition calculated taking the values in the control group as 100%. Since a maximum of 60 - 70% inhibition (paw edema) was obtained with standard NSAIDs, ED_{30} values were used for comparison. All treatment groups were coded to eliminate observer bias. With this protocol, the ED_{30} for Indomethacin is 1.0 mg/kg. Representative results are shown in Table IV.

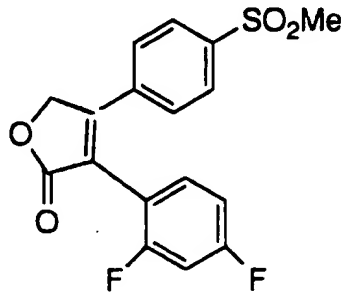
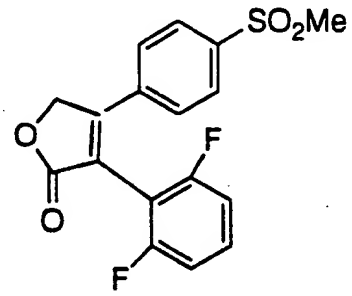
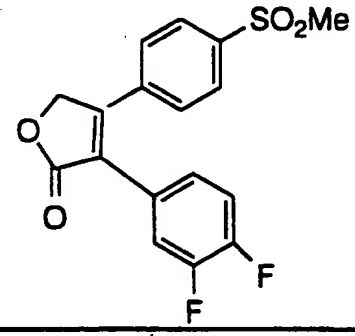
Example	Conc. (nM)	COX-2 % inhib.	COX-1 % inhib.		Conc. (nM)	COX-2 % inhib.	COX-1 % inhib.
15	20	39					
15	80	76					
15	160	95					
16	20	41					
16	40	50					
16	160	85					
17	40	41					
17	160	77					
18	40	24					
18	160	58					
19	40	21					
19	160	59					
20	10	70					
20	40	91					
21	10	50					
21	40	94					
22	20	39					
22	160	98					
23	20	50					
23	160	88					
24	40	43					
24	160	78					
25	160	40					
26	80	27					
26	160	39					
27	20	38					
27	160	97					

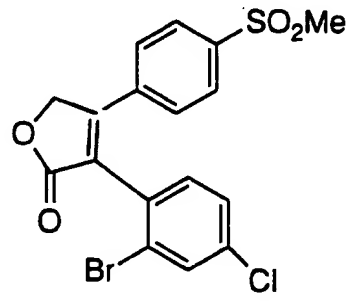
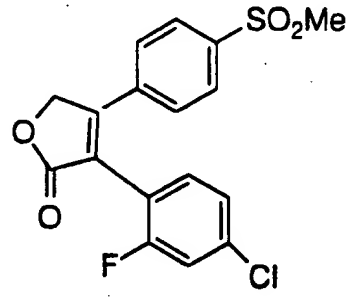
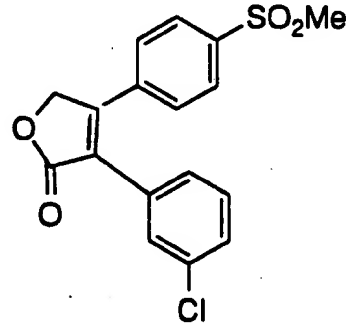
Example	Conc. (nM)	COX-2 % inhib.	COX-1 % inhib.		Conc. (nM)	COX-2 % inhib.	COX-1 % inhib.
39	160	84					
40	10	43					
40	40	72					
40	160	96					
41							
41							
42	20	10					
42	160	44					
43	10	78					
43	40	101					
44	20	14					
44	40	55					
44	160	106					
45	10	16					
45	40	61					
45	160	101					
46	10	76					
46	40	94					
46	160	97					
47	10	61					
47	40	74					
47	160	101					
48	10	7					
48	160	47					
49	10	53					
49	40	91					
49	80	99					
50	80	42					

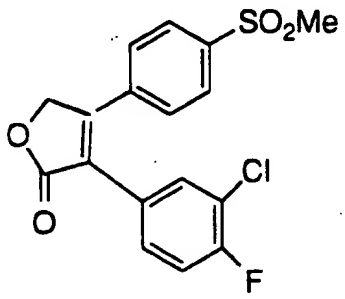
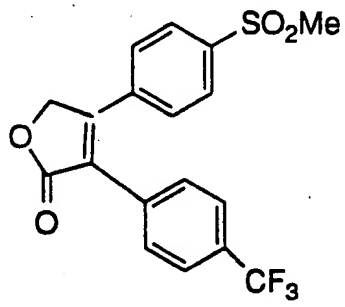
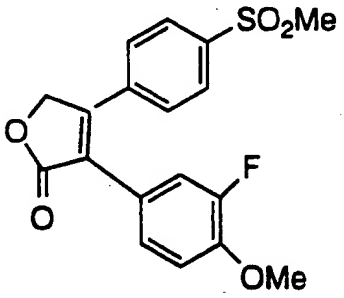
TABLE IV

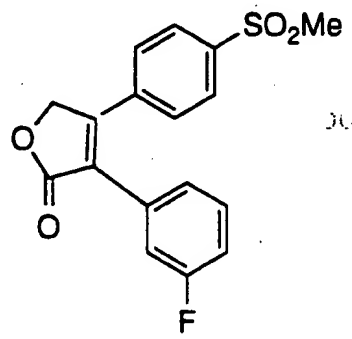
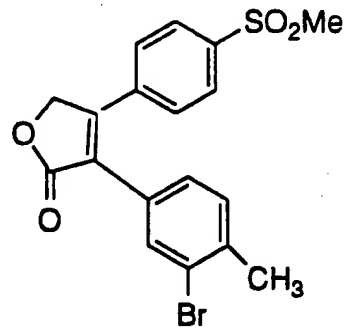
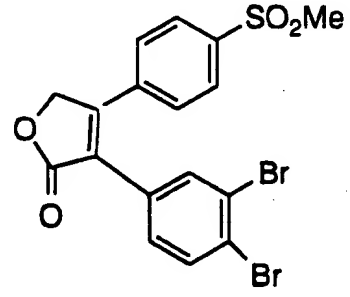
ED30(mg/kg)	STRUCTURE
~3.00	
>10.00	

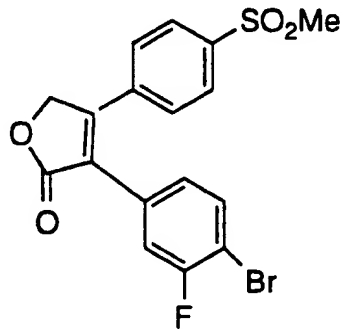
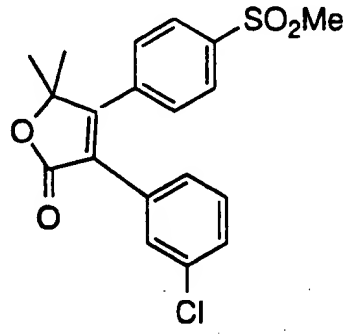
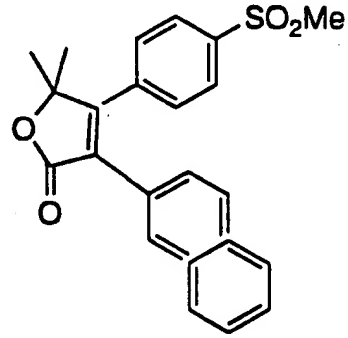
~3.00	
>3.00 3.00	
1.10	

2.03	
1.49	
0.35	

0.88	
0.47	
0.71	

0.43	
2.17	
0.81	

0.33	
0.46	
0.76	

0.55	
0.25	
0.1-.3	

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C; the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations; the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data; yields are given for illustration only; when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal; chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

The following abbreviations have the indicated meanings:

Ac	=	acetyl
Bn	=	benzyl
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	=	diisobutylaluminum hydride
DMAP	=	4-(dimethylamino)pyridine

Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

Step 3: 5-(4-Fluorophenyl)-4-(4-(methylthio)phenyl)thiophene-2-carboxylic acid methyl ester

To a solution of cis,trans 3-chloro-3-(4-fluorophenyl)-2-(4-(methylthio)phenyl)propenal (3.00 g) in pyridine (12.0 mL) were added methyl thioglycolate (1.16 mL) and Et_3N (4.09 mL). The resulting mixture was then heated at 80°C for 2 h. After extraction with EtOAc and washing with 3N HCl, the title product was purified by flash chromatography (30% EtOAc in hexane) (2.00 g).
^1H NMR (CD_3COCD_3): δ 2.48 (3H, s), 3.88 (3H, s), 7.11 (2H, t), 7.21 (4H, s), 7.37 (2H, q), 7.80 (1H, s).

Step 4: 5-(4-Fluorophenyl)-4-(4-(methylsulfinyl)phenyl)thiophene-2-carboxylic acid methyl ester

To a solution of 5-(4-fluorophenyl)-4-(4-(methylthio)phenyl)-thiophene-2-carboxylic acid methyl ester (5.60 g) in CH_2Cl_2 (84.0 mL) at 0°C was added portionwise m-CPBA 50 to 60% (5.39 g). After TLC showed completion (50% EtOAc in hexane), the reaction mixture was extracted with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to dryness to provide the title compound as a white foam (5.00 g).
^1H NMR (CD_3COCD_3): δ 2.75 (3H, s), 3.92 (3H, s), 7.15 (2H, t), 7.40 (2H, q), 7.52 (2H, d), 7.66 (2H, d), 7.90 (1H, s).

Step 5: 4-(4-(Aminosulfonyl)phenyl)-5-(4-fluorophenyl)thiophene-2-carboxylic acid methyl ester

5-(4-Fluorophenyl)-4-(4-(methylsulfinyl)phenyl)thiophene-2-carboxylic acid methyl ester (0.500 g) was dissolved in TFAA (10.0 mL) and refluxed for 0.5 h. The solvent was then removed *in vacuo* and the resulting residue was co-evaporated 10 times with a Et_3N-MeOH solution (1:1) (100.0 mL) to provide a viscous oil after pumping for a few hours. The oil was dissolved in HOAc (10.0 mL) and treated at +10°C with Cl_2 in

(0.210 g) in THF (2.0 mL) were added MeOH (1.0 mL), NaOH 1N (1.0 mL) and a few drops of NaOH 10N. The resulting mixture was heated at 45°C for 2 h and the reaction was then partitioned between EtOAc and HCl (3N) to provide the title product as a white solid (0.200 g).
^{1}H NMR (CD_3COCD_3) δ 6.60 (2H, s), 7.15 (2H, t), 7.35 (2H, q), 7.45 (2H, d), 7.82 (2H, d), 7.87 (1H, s).

Step 2: 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene

To a solution of 3-(4-(aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene-2-carboxylic acid (0.280 g) in quinoline (4.0 mL) was added Cu bronze (0.300 g). After 0.5 h at 180°C under nitrogen, the reaction mixture was extracted with EtOAc and HCl 3N, dried over Na_2SO_4 and purified by flash chromatography (30% EtOAc in hexane) to give the title compound as a white solid (0.180 g).
^{1}H NMR (CD_3COCD_3): δ 6.60 (2H, bs), 7.15 (2H, t), 7.29 (1H, d), 7.35 (2H, q), 7.45 (2H, d), 7.60 (1H, d), 7.83 (2H, d).

Anal. calcd for $C_{16}H_{12}FNO_2S_2$;
C, 57.65; H, 3.60; N, 4.20.
Found: C, 57.62; H, 3.59; N, 4.15.

EXAMPLE 3

3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene

^{1}H NMR (CD_3COCD_3) δ 1.40 (6H, d), 3.25 (1H, septuplet), 6.58 (2H, bs), 7.05 (1H, s), 7.15 (2H, t), 7.32 (2H, dd), 7.46 (2H, d), 7.80 (2H, d).

Anal. calcd. for $C_{19}H_{18}FNO_2S_2$.
C, 60.80; H, 4.80; N, 3.73.
Found: C, 60.59; H, 4.45; N, 3.60.

(20.0 mL) at 0°C. After a few hours at r.t., the reaction mixture was extracted with EtOAc and H_2O to afford after flash chromatography (50 to 100% EtOAc in hexane), the title product as a white solid (3.20 g).
^1H NMR (CD_3COCD_3) δ 3.10 (3H, s), 3.95 (3H, s), 4.65 (2H, s), 7.60 (2H, d), 7.96 (2H, d), 8.20 (4H, q).

Step 3: Cis,trans 4-(1-Chloro-3-oxo-2-(4-(methylsulfonyl)phenyl)-1-propenyl)benzoic acid methyl ester

To a solution of 4-(1-oxo-2-((4-methylsulfonyl)phenyl)ethyl) benzoic acid (1.70 g) in 1,2-dichloroethane (15.0 mL) were added the Vilsmeier reagent 3.3 M (6.2 mL) and DMAP (0.624 g). The resulting mixture was heated at 80°C for 4 h. The reaction mixture was then extracted with 25% aqueous solution of NH_4OAc and EtOAc. After drying over Na_2SO_4 and evaporation the title compound was obtained as an oil and used as such for the next step.

Step 4: 5-(4-(Methoxycarbonyl)phenyl)-4-(4-(methylsulfonyl)-phenyl)thiophene-2-carboxylic acid methyl ester

Prepared from 4-(1-chloro-3-oxo-2-(4-methylsulfonyl)-phenyl)-1-propenyl)benzoic acid methyl ester as for Example 1, Step 3.
^1H NMR (CD_3COCD_3) δ 3.13 (3H, s), 3.85 and 3.92 (6H, 2s), 7.50 (2H, d), 7.55 (2H, d), 7.90 (2H, d), 7.92 (1H, s), 7.92 (2H, d).

Step 5: 5-(4-(Carboxyphenyl)-4-(4-(methyl)sulfonyl)phenyl)-thiophene-2-carboxylic acid

Prepared from 5-(4-(methoxycarbonyl)phenyl)-4-(4-(methyl)sulfonyl)phenyl) thiophene-2-carboxylic acid methyl ester as for Example 2, Step 1.
^1H NMR (CD_3COCD_3) δ 3.15 (3H, s), 7.50 (2H, d), 7.62 (2H, d), 7.95 (2H, d), 7.98 (1H, s), 8.05 (2H, d).

Anal calcd. for $C_{19}H_{14}O_6S_2 \cdot 0.1\ H_2O$:

Step 3: 4-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)-thiazole

To 2-bromo-1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-ethanone (1.10 g) in ethanol (15.0 mL) were added thioacetamide (0.266 g) and pyridine (0.300 mL). After refluxing for 2 h, the reaction mixture was extracted with EtOAc, 25% NH_4OAc and purified by flash chromatography (50% EtOAc in hexane then 90% Et_2O in hexane) to yield the title compound (0.320 g).

^1H NMR (CD_3COCD_3) δ 2.72 (3H, s), 3.15 (3H, s), 7.09 (2H, t), 7.52 (2H, dd), 7.60 (2H, d), 7.92 (2H, d).

Anal. calcd. for $C_{17}H_{14}FNO_2S_2$:
C, 58,78; H, 4.03; N, 4.03.
Found: C, 58.71, H, 4.17; N, 3.85.

EXAMPLE 7

2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

Step 1: 1-(4-Fluorophenyl)-5-hexen-2-one

To a suspension of 14.6 g (80 mmol) of $CdCl_2$ in 200 mL of ether cooled to 0°C was added 115 mL of 1.3 M solution of 3-butene-1-magnesium bromide dropwise. The mixture was refluxed for 1 h and ether was then removed by distillation. Benzene (500 mL) was introduced, followed by a solution of 17.5 g (100 mmol) 4-fluorophenylacetyl chloride. After refluxing for 1 h, the reaction mixture was quenched with 200 mL of saturated aqueous NH_4Cl, 50 mL of 1 N HCl, and extracted with 200 mL of 1:1 hexane/EtOAC. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography eluted with 4:1 hexane/EtOAc to give 15 g of the title product.

^1H NMR ($CDCl_3$) δ 2.40 (2H, t), 2.53 (2H, t), 3.63 (2H, s), 4.90-4.98 (2H, m), 5.67-5.78 (1H, m), 6.98 (2H, t), 7.13 (2H, m).

^{1}H NMR ($CDCl_3$) δ 2.12 (1H, s), 2.34 (2H, m), 2.44 (3H, s), 2.45-2.52 (1H, m), 2.56-2.65 (1H, m), 6.37 (1H, m), 6.84 (2H, J=8.7 Hz, t), 7.17 (2H, J=8.3 Hz, d), 7.24-7.33 (4H, m).

Step 5: 2-(4-Fluorophenyl)-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one

To a suspension of PCC (4.5 g, 20.9 mmol) and 10 g of anhydrous 4Å molecular sieves in 150 mL of CH_2Cl_2 was added a solution of 2.2 g (7.3 mmol) of 1-(4-(methylthio)phenyl)-2-(4-fluorophenyl)-2-cyclopenten-1-ol in 20 mL CH_2Cl_2. The mixture was stirred for 1 h at r.t. and then diluted with 300 mL of Et_2O. After filtration and concentration, the residue was flash chromatographed with 2:1 hexane/EtOAc to give 1.5 g of the title product.

^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s), 2.68 (2H, m), 3.00 (2H, m), 7.02 (2H, J=8.6 Hz, t), 7.11 (2H, J=8.6 Hz, d), 7.15-7.23 (4H, m).

Step 6: 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a solution of 50 mg (0.17 mmol) of 2-(4-Fluorophenyl)-3-(4-methylthio)phenyl)-2-cyclopenten-1-one in 8 mL of 10:1 CH_2Cl_2/MeOH was added 124 mg (0.2 mmol) of MPPM. The reaction mixture was stirred at room temperature for 2 h and then diluted with 10 mL of 1:1 hexane/EtOAc. After filtration and concentration, the residue was purified by flash chromatography eluted with 2:1 EtOAc/hexane to give 45 mg of the title product.

^{1}H NMR (acetone-d_6) δ 2.67 (2H, m), 3.14 (3H, s), 3.16 (2H, m), 7.05-7.10 (2H, m), 7.20-7.25 (2H, m), 7.63 (2H, d), 7.93 (2H, d).

EXAMPLE 8

4-(4-(Methylsulfonyl)phenyl)-5-(4-fluorophenyl)-isothiazole

Step 2:

To the product of Step 1 (216 mg) dissolved in acetonitrile (4 mL) was added Et3N (0.26 mL), followed by 4-fluorophenylacetic acid (102 mg). After 1.5 h at room temperature 0.23 mL of DBU was added. The reaction mixture was stirred for another 45 min and then treated with 5 mL of 1N HCl. The product was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (40% EtOAc in hexane) to yield 150 mg of the title compound as a solid.

^{1}H NMR (CD_3COCD_3) δ 3.15 (3H, s), 5.36 (3H, s), 7.18 (2H, J=8.9 Hz, t), 7.46 (2H, m), 7.7 (2H, J=8.65 Hz, d), 7.97 (2H, J=8.68, d).

EXAMPLE 10

3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*2H*)-furanone

^{1}H NMR (CD_3COCD_3) δ 5.34 (2H, s), 6.67 (2H, bd), 7.18 (2H, m), 7.46 (2H, m), 7.61 (2H, m), 7.90 (2H, m).
M.P. 187-188 °C (d).

EXAMPLE 11

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan

Step 1:

Using the product of Example 10, (0.2 g) in THF (5 mL) and toluene (3 mL) was added slowly at -78°C a solution of DIBAL (0.72 mL, 1M in toluene). After 15 min, the solution was warmed up to 0°C for another 15 min. This mixture was then poured into a chilled aqueous solution of sodium potassium tartrate and EtOAc. The organic layer was stirred for 0.5 h with a few crystals of camphor sulfonic acid. This

Step 3: 2-Hydroxy-4'-(methylthio)isobutyrophenone

To a solution of 40 mg (0.14 mmol) of 2-trimethylsilyloxy-4'-(methylthio)isobutyrophenone in 2 mL THF was added 0.2 mL of 1 M n-Bu4NF in THF. The resulting mixture was stirred for 30 min and then quenched with 10 mL of NH4OAc buffer. The product was extracted with EtOAc, dried over MgSO4 and concentrated. The residue was purified by flash chromatography, eluting with 4:1 hexane/EtOAc to give 25 mg of the title product.

^{1}H NMR (CD_3COCD_3) δ 1.50 (6H, s), 2.54 (3H, s), 4.68 (1H, s), 7.30 (2H, d), 8.15 (2H, d).

Step 4: 2-(4-Fluorophenylacetoxy)-4'-(methylthio)isobutyrophenone

To a solution of 72 mg (0.34 mmol) 2-hydroxy-4'-(methylthio)isobutyrophenone in 1.7 mL of CH_2Cl_2 were added 0.2 mL of pyridine and 140 mg (0.81 mmol) of 4-fluorophenylacetyl chloride. The mixture was stirred at room temperature overnight and then quenched with NH4OAc buffer. The product was extracted with EtOAc, dried over MgSO4 and concentrated. The crude product was purified by flash chromatography eluting with 8:1 hexane/EtOAc to give 95 mg of the title product.

^{1}H NMR (CD_3COCD_3) δ 1.62 (3H, s), 1.67 (3H, s), 2.48 (3H, s), 3.79 (2H, s), 7.0-7.3 (6H, m), 7.78 (2H, d).

Step 5: 5,5-Dimethyl-3-(4-fluorophenyl-4-(4-methylthiophenyl)-2-(*5H*)-furanone

To a solution of 95 mg of 2-(4-fluorophenylacetoxy)-4'-(methylthio)-isobutyrophenone in 4 mL of CH_2Cl_2 was added 0.2 mL of 1,8-diazabicyclo(5.4.0)undec-7-ene. The mixture was stirred for 4 h and diluted with NH4OAc buffer. The product was extracted with EtOAc, dried over MgSO4 and concentrated. The residue was purified by flash

^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.15 (2H, t), 7.30 (3H, m), 7.45 (2H, d), 7.65 (1H, d), 7.95 (2H, d).

EXAMPLE 15

3-(2,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

Analysis	calculated for $C_{17}H_{12}F_2O_4S$
	C, 58.28; H, 3.45; S, 9.15
Found:	C, 58.27; H, 3.50; S, 9.27

EXAMPLE 16

3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone

To a solution of 3,4-difluorophenylacetic acid (ALDRICH CHIMICAL) (10 g) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 9, Step 1) (17.3 g) in acetonitrile (200 mL) at room temperature was added slowly triethylamine (20.2 mL). After 1 h at room temperature, the mixture was cooled in an ice bath and treated with 17.4 mL of DBU. After 2 h at 0°C, the mixture was treated with 200 mL of 1N HCl and the product was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was applied on top of a silica gel plug (sintered glass funnel) eluted with 75% EtOAc/hexane, giving after evaporation of the solvent and swish in ethyl acetate, 10 g of the title compound.

Analysis	calculated for $C_{17}H_{12}F_2O_4S$
	C, 58.28; H, 3.45; S, 9.15
Found:	C, 58.02; H, 3.51; S, 9.35

EXAMPLE 17

3-(4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (2H, d), 7.49 (2H, d), 7.35 (4H, m), 5.16 (2H, s), 3.06 (3H, s)

EXAMPLE 22

3-(4-Methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis	calculated for $C_{18}H_{16}O_5S$
	C, 62.78 H, 4.68; S, 9.31
Found:	C, 62.75; H, 4.72; S, 9.39

EXAMPLE 23

3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

To a solution of phenylacetic acid (27.4 g, 201 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (Example 9, Step 1) (60 g, 216 mmol, 1.075 eq.) in acetonitrile (630 mL) at 25°C was added slowly triethylamine (30.8 mL, 1.1 eq.). The mixture was stirred for 20 min. at room temperature and then cooled in an ice bath. DBU (60.1 mL, 3 eq.) was slowly added. After stirring for 20 min. in the ice bath, the reaction was complete and the mixture was acidified with 1N HCl (color changes from dark brown to yellow). Then 2.4 L of ice and water were added, stirred for a few minutes, then the precipitate was filtered and rinsed with water (giving 64 g of crude wet product). The solid was dissolved in 750 mL of dichloromethane (dried over $MgSO_4$, filtered) and 300 g of silica gel was added. The solvent was evaporated to near dryness (silica gel a bit sticky) and the residue was applied on top of a silica gel plug (sintered glass funnel) eluted with 10% EtOAc/CH_2Cl_2, giving after evaporation of the solvent and swish in ethyl acetate, 36.6 g (58%) of the title compound.

3-(4-Chloro-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

^{1}H NMR (300 MHz, acetone-d_6) δ 8.0 (2H, d), 7.70 (2H, d), 7.50-7.30 (3H, m), 5.35 (2h, s), 3.15 (3H, s)

EXAMPLE 28

3-(3-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis	calculated for $C_{17}H_{12}BrFO_4S$
	C, 49.75; H, 2.93
Found:	C, 49.44; H, 2.98

EXAMPLE 29

3-(3-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis	calculated for $C_{17}H_{13}ClO_4S$
	C, 58.54; H, 3.76
Found:	C, 58.29; H, 3.76

EXAMPLE 30

3-(2-Chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis	calculated for $C_{17}H_{12}ClFO_4S$
	C, 55.67; H, 3.30
Found:	C, 55.67; H, 3.26

EXAMPLE 35

3-(4-Trifluoromethylphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

^{1}H NMR (CD_3COCD_3) δ 8.10 (2H, d), 7.82-7.93 (4H, m), 7.75 (2H, d), 5.55 (2H, s), 3.30 (3H, s)

EXAMPLE 36

3-(3-Fluoro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{18}H_{15}FO_5S$
C, 59.66; H, 4.17
Found: C, 59.92; H, 4.37

EXAMPLE 37

3-(3-Chloro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{18}H_{15}ClO_5S$
C, 57.07; H, 3.99
Found: C, 57.29; H, 4.15

EXAMPLE 38

3-(3-Bromo-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{18}H_{15}BrO_5S$

EXAMPLE 43

3-(3-Bromo-4-methylphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{18}H_{15}BrO_4S$
C, 53.08; H, 3.71
Found: C, 53.06; H, 3.83

EXAMPLE 44

3-(4-Bromo-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}BrFO_4S$
C, 49.65; H, 2.94
Found: C, 49.76; H, 3.00

EXAMPLE 45

3-(3,4-Dibromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

$_1$H NMR (300 MHz, acetone-d_6) δ 8.0 (2H, d), 7.80 (1H, d), 7.75 (3H, m), 7.25 (1H, d), 5.35 (2H, s), 3.15 (sH, s)

EXAMPLE 46

3-(4-Chloro-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone

Analysis calculated for $C_{17}H_{12}ClFO_4S$

Analysis calculated for $C_{20}H_{15}NO_4S$
C, 65.74; H, 4.14; N, 3.83
Found: C, 65.34; H, 4.40; N, 3.80
M.S. (DCI, CH_4) calculated for M^+, 365
Found for M^++1, 366

EXAMPLE 51

3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.92 (2H, dd), 7,64 (3H, dm), 7.60 (1H, dd), 7.32 (1H, dd), 6.70 (1H, bs), 5.38 (2H, s)

EXAMPLE 52

3-(3,4-Difluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.92 (2H, dd), 7,64 (2H, dd), 7.30-7.45 (2H, m), 7.22 (1H, m), 6.68 (2H, bs), 5.37 (2H, s)

EXAMPLE 53

3-(3-Chloro-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(2*H*)-furanone

Analysis calculated for $C_{17}H_{14}ClNO_5S$
C, 53.76; H, 3.72, N, 3.69
Found: C, 53.32; H, 3.84, N, 3.59
M.S. (DCI, CH_4) calculated for M^+, 379
Found for M^++1, 380

To a solution of 3.86 g (19 mmol) of 4-bromothioanisole in 90 mL of Et_2O cooled at -78°C, is added 22 mL of 1.7 M solution of t-BuLi in pentane (38 mmol) dropwise. The reaction mixture is stirred for 15 min at -78°C and 3.8 g of CuI is added and the reaction mixture is allowed to warm to -40 °C over a period of 30 min. A solution of 1.7 g of 2(*5H*)-furanone in 10 ml of THF is added. After stirring for 1 h, 2 ml of freshly distilled TMSCl is added dropwise. The reaction mixture is then treated with 2 ml of Et_3N and 50 ml of sat. $NaHCO_3$, and extracted with 100 ml of ether. The ether layer is dried over Na_2SO_4 and concentrated to the crude title compound which is used for the next step without further purification.

Step 2: 4-(4-(methylthio)phenyl)-2-(*5H*)-furanone

To a solution of 4 g of $Pd(OAc)_2$ in 100 ml of acetonitrile is added dropwise the crude product from Step 1(5 g) under nitrogen at room temperature. After 10 h at room temperature, the mixture is condensed under reduced pressure and the residue is purified by flash chromatography on silica gel eluted with 2:1 hexane/EtOAc to give the title compound.

Step 3: 3-iodo-4-(4-(methylthio)phenyl)-2-(*5H*)-furanone

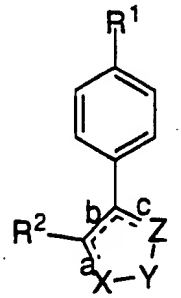
To a solution of 3 g of the product of Step 2 in 30 ml of pyridine is added 8.7 g of I_2. The mixture is stirred for 24 h and then diluted with 200 ml of ether, washed with 100 ml of 5N HCl and 50 ml of 5N $Na_2S_2O_3$. The ether layer is dried over Na_2SO_4 and concentrated to give the title compound.

Step 4: 3-(Phenyl)-4-(4-(methylthio)phenyl)-2-(*5H*)-furanone

A mixture of 4 g of the product of Step 3, 3.7 g of $PhB(OH)_2$, 0.4 g of Ph_3As, 0.4 g of $PdCl_2(PhCN)_2$ in 100 ml of benzene and 15 ml of

WHAT IS CLAIMED IS:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein:
X–Y–Z–is selected from the group consisting of:

(a) -$CH_2CH_2CH_2$-,
(b) -$C(O)CH_2CH_2$-,
(c) -$CH_2CH_2C(O)$-,
(d) -$CR^5(R^{5'})$-O-C(O)-,
(e) -C(O)-O-$CR^5(R^{5'})$-,
(f) -CH_2-NR^3-CH_2-,
(g) -$CR^5(R^{5'})$-NR^3-C(O)-,
(h) -CR^4=$CR^{4'}$-S-,
(i) -S-CR^4=$CR^{4'}$-,
(j) -S-N=CH-,
(k) -CH=N-S-,
(l) -N=CR^4-O-,
(m) -O-CR4=N-
(n) -N=CR^4-NH-,
(o) -N=CR^4-S-, and
(p) -S-CR^4=N-,
(q) -C(O)-NR^3-$CR^5(R^{5'})$-,

(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of
(1) hydrogen,
(2) halo, including fluoro, chloro, bromo and iodo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$,
(10) $-C(R^5)(R^6)-O-C_{1-4}$alkyl;

R^3 is selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) CN,

(a) hydrogen,
(b) C_{1-6}alkyl,
or R^5 and R^6 or R^7 and R^8 together with the carbon to which they are attached form a monocyclic saturated carbon ring of 3, 4, 5, 6 or 7 atoms;

Q is CO_2H, CO_2-C_{1-4}alkyl, tetrazolyl-5-yl, $C(R^7)(R^8)(OH)$, or $C(R^7)(R^8)(O$-C_{1-4}alkyl),

provided that when X-Y-Z is -S-CR^4= $CR^{4'}$, then R^4 and $R^{4'}$ are other than CF_3 .

2. A compound according to Claim 1 wherein X–Y–Z–is selected from the group consisting of:
(a) -$CH_2CH_2CH_2$-,
(b) -$C(O)CH_2CH_2$-,
(c) -$CH_2CH_2C(O)$-,
(d) -$CR^5(R^{5'})$-O-C(O)-,
(e) -C(O)-O-$CR^5(R^{5'})$-,
(f) -CH_2-NR^3-CH_2-,
(g) -$CR^5(R^{5'})$-NR^3-C(O)-,
(h) -CR^4=$CR^{4'}$-S-,
(i) -S-CR^4=$CR^{4'}$-,
(j) -S-N=CH-,
(k) -CH=N-S-,
(l) -N=CR^4-O-,
(m) -O-CR4=N-
(n) -N-CR^4-NH-,
(o) -N=CR^4-S-, and
(p) -S-CR^4=N-,
(q) -C(O)-NR^3-$CR^5(R^{5'})$-,
(r) -NR^3-CH=CH- provided R^1 is other than -$S(O)_2$Me,

(6) oxadiazolyl,
(7) oxazolyl,
(8) pyrazolyl,
(9) pyrrolyl,
(10) thiadiazolyl,
(11) thiazolyl,
(12) thienyl,
(13) triazolyl, and
(14) tetrazolyl,

wherein said substituents are selected from the group consisting of

(a) hydrogen,
(b) fluoro, chloro, bromo,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) CN,
(5) CF_3,
(6) C_{1-4}alkyl,
(7) N_3,
(8) $-C(R^5)(R^6)-OH$,
(9) $-C(R^5)(R^6)-O-C_{1-4}$alkyl.

3. A compound according to Claim 2 wherein R^2 is selected from the group consisting of

(a) cyclohexyl, and
(b) mono- or di-substituted phenyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,
(5) CN,

mono or di-substituted phenyl wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo,

(3) methoxy, and

(4) methyl.

5. A compound according to claim 4 wherein

X–Y–Z–is selected from the group consisting of:

(a) -CH_2-O-C(O)-, and

(b) -C(O)-O-CH_2-, and

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and

(b) $S(O)_2NH_2$,

R^2 is

mono or di-substituted phenyl wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo, selected from the group consisting of fluoro, chloro and bromo.

6. A compound according to Claim 2 wherein

R^2 is a mono- or di-substituted heteroaryl wherein heteroaryl is selected from the group consisting of

(1) furanyl,

(2) diazinyl, triazinyl, tetrazinyl,

(3) imidazolyl,

(4) isooxazolyl,

(5) isothiazolyl,

(6) oxadiazolyl,

(7) oxazolyl,

(12) 1,4-diazinyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) fluoro or chloro,

(3) C_{1-3}alkoxy,

(4) C_{1-3}alkylthio,

(5) CN,

(6) C_{1-3}alkyl, and

(7) $-C(R^5)(R^6)-OH$,

wherein R5 and R6 are each independently hydrogen, methyl or ethyl.

8. A compound according to claim 7 wherein

X–Y–Z–is selected from the group consisting of:

(a) $-CH_2-O-C(O)-$,

(b) $-C(O)-O-CH_2-$, and

(c) $-CH_2-NR^3-C(O)-$;

R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)NHCH_3$, and

(d) $S(O)NHNH_2$, and

R^3 is selected from the group consisting of

(a) hydrogen,

(b) CF_3,

(c) C_{1-3}alkyl and hydroxyC_{1-3}alkyl,

(d) CN, and

the hetereooaryl is selected from the group consisting of

(1) 3-isothiazolyl,

(2) 4-isothiazolyl,

(3) 5-isothiazolyl,

(4) 2-oxazolyl,

(e) $S(O)(NH)NH_2$, and

(f) $S(O)(NH)NHC(O)CF_3$;

R^2 is selected from the group consisting of

(a) C_{1-4}alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of

(1) hydrogen,

(2) fluoro, chloro, and bromo,

(3) C_{1-4}alkoxy,

(4) C_{1-4}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-4}alkyl,

(8) N_3,

(9) $-CO_2H$,

(10) $-CO_2-C_{1-3}$alkyl,

(10) $-C(R^5)(R^6)-OH$, and

(11) $-C(R^5)(R^6)-O-C_{1-3}$alkyl,

(d) mono- or di-substituted heteroaryl selected from the group consisting of

(1) furanyl,

(2) diazinyl, triazinyl and tetrazinyl,

(3) imidazolyl,

(4) isooxazolyl,

(5) isothiazolyl,

(6) oxadiazolyl,

(7) oxazolyl,

(8) pyrazolyl,

(9) pyrrolyl,

(10) thiadiazolyl,

(11) thiazolyl,

(b) CF_3,
(c) C_{1-3}alkyl and hydroxyC_{1-3}alkyl,
(d) CN;

R^5, $R^{5'}$, R^6, are each independently selected from the group consisting of
(a) hydrogen,
(b) methyl or ethyl,
or R^5 and R^6 together with the carbon to which they are attached form a saturated carbon ring of 4, 5 or 6 atoms.

11. A compound according to claim 10 wherein
X–Y–Z–is selected from the group consisting of:
(a) =CH-O-CH=,
(b) =N-S-N=,
(c) =N-O-N=;

R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$;

R^2 is selected from the group consisting of
mono- or di-substituted phenyl wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo, selected from the group consisting of fluoro, chloro and bromo,
(3) C_{1-3}alkoxy,
(4) C_{1-3}alkylthio,
(5) CF_3,
(6) C_{1-3}alkyl;

R^3 is selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) C_{1-3}alkyl and hydroxyC_{1-3}alkyl,

R^5 and R^6 are each selected from the group consisting of

(11) thiazolyl,
(12) thienyl,
(13) triazolyl,
(15) pyridyl, and
(16) tetrazolyl, and

wherein the substitutents are selected from the group consisting of

(a) hydrogen,
(b) fluoro or chloro,
(c) C_{1-3}alkoxy,
(d) C_{1-6}alkylthio,
(e) CN,
(5) CF_3,
(6) C_{1-3}alkyl,
(7) $-C(R^5)(R^6)-OH$;
(8) $-C(R^5)(R^6)-O-C_{1-4}$alkyl.

14. A compound according to Claim 13 wherein R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$, and
(b) $S(O)_2NH_2$, and

the hetreoaryl is selected from the group consisting of

(1) 3-isothiazolyl,
(2) 4-isothiazolyl,
(3) 5-isothiazolyl,
(4) 2-oxazolyl,
(5) 4-oxazolyl,
(6) 5-oxazolyl,
(7) 2-thiazolyl,
(8) 4-thiazolyl,
(9) 5-thiazolyl,
(10) 1,2-diazinyl,

(12) 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(13) 2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)thiophene, and
(14) 3-(4-(Trifluoroacetylaminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,
(15) 3-(2,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(16) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(17) 3-(2,6-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(18) 3-(2,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(19) 3-(3,5-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(20) 3-(4-Bromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(21) 3-(4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(22) 3-(4-Methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(23) 3-(Phenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(24) 3-(2-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(25) 3-(2-Bromo-4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(26) 3-(2-Bromo-4-Chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(27) 3-(4-Chloro-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(44) 3-(4-Bromo-2-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(45) 3-(3,4-Dibromophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(46) 3-(4-Chloro-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(47) 3-(4-Bromo-3-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(48) 3-(4-Bromo-2-chlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(49) 3-(2-Naphthyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(50) 3-(7-Quinolinyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(51) 3-(3,4-Dichlorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*2H*)-furanone,
(52) 3-(3,4-Difluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*2H*)-furanone,
(53) 3-(3-Chloro-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*2H*)-furanone, and
(54) 3-(3-Bromo-4-methoxyphenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*2H*)-furanone.

16. A compound which is
(a) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone, or
(b) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
or a pharmaceutically acceptable salt thereof.

(e) $S(O)(NH)NH_2$, and

(f) $S(O)(NH)NHC(O)CF_3$,

R^2 is selected from the group consisting of

mono- or di-substituted phenyl, and

wherein the substitutents are selected from the group consisting of

(1) hydrogen,

(2) halo,

(3) C_{1-4}alkoxy,

(4) C_{1-4}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-4}alkyl,

(8) N_3, and

(9) $-C(R^5)(R^6)-OH$;

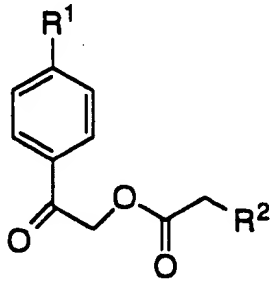
R^5 and R^6, are each independently selected from the group consisting of

(a) hydrogen,

(b) methyl or ethyl,

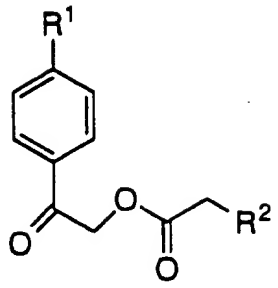
or R^5 and R^6 together with the carbon to which they are attached form a saturated carbon ring of 4, 5 or 6 atoms;

treating in a non-aqueous polar solvent a compound for formula A



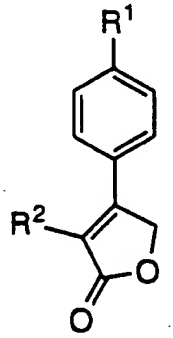
A

in the presence of a strong base;



A

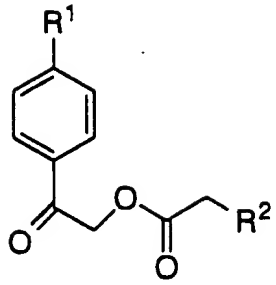
(b) treating in a non-aqueous polar solvent a compound of formula A with strong base to yield a compound of formula XXXIII



XXXIII

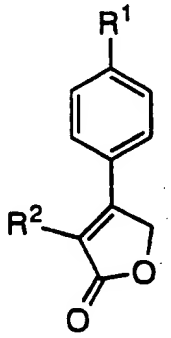
21. A process according to Claim 20 comprising:

(a1) reacting in an organic solvent a compound of formula XXXII'



A

(a3) treating in a non-aqueous polar solvent a compound of formula A with strong base to yield a compound of formula XXXIII



XXXIII

22. A process according to claim 21 wherein R^1 is selected from the group consisting of

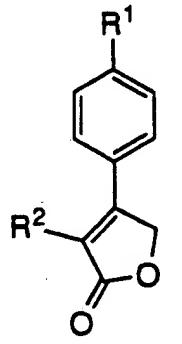
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)NHCH_3$, and
(d) $S(O)NHNH_2$;

R^2 is

(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-4}alkyl,
(8) N_3, and
(9) $-C(R^5)(R^6)-OH$;

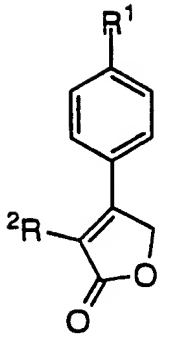
R^5 and R^6, are each independently selected from the group consisting of
(a) hydrogen,
(b) methyl or ethyl,
or R^5 and R^6 together with the carbon to which they are attached form a saturated carbon ring of 4, 5 or 6 atoms.

24. A process of making a compound of formula XXXIII

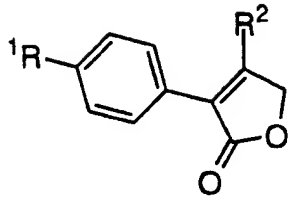


XXXIII

wherein
R^1 is selected from the group consisting of
(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHC(O)CF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$, and

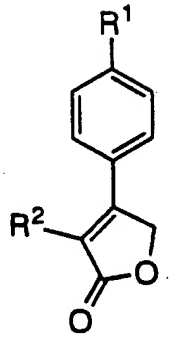


XXXIII



XXXV

25. A process of making a compound of formula XXXIII



XXXIII

wherein
R^1 is $S(O)_2CH_3$,
R^2 is selected from the group consisting of
mono- or di-substituted phenyl, and
wherein the substitutents are selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-4}alkoxy,
(4) C_{1-4}alkylthio,

NOT TO BE TAKEN
INTO CONSIDERATION
FOR THE PURPOSES
OF INTERNATIONAL PROCESSING

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 277/02, 275/02, 307/02, 333/04
A61K 31/33, C07C 305/18, 307/02

A3

(11) International Publication Number: WO 95/00501

(43) International Publication Date: 5 January 1995 (05.01.95)

(21) International Application Number: PCT/CA94/00318

(22) International Filing Date: 9 June 1994 (09.06.94)

(30) Priority Data:

082,196	24 June 1993 (24.06.93)	US
179,467	10 January 1994 (10.01.94)	US

(60) Parent Application or Grant
(63) Related by Continuation
US 179,467 (CIP)
Filed on 10 January 1994 (10.01.94)

(71) Applicant *(for all designated States except US)*: MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DUCHARME, Yves [CA/CA]; 4501 Kensington, Montreal, Quebec H4B 2W6 (CA). GAUTHIER, Jacques, Yves [CA/CA]; Apartment 2, 540 Odette Oligny, Laval, Quebec H7N 5Z4 (CA). PRASIT, Petpiboon [CA/CA]; 177 Argyle Drive, Kirkland, Quebec H9H 5A6 (CA). LEBLANC, Yves [CA/CA]; 8 Lafford, Kirkland, Quebec H9J 3Y3 (CA). WANG, Zhaoyin [CA/CA]; 13199 Edison Crescent, Pierrefonds, Quebec H8Z 1Y5 (CA). LEGER, Serge [CA/CA]; 51 Lamarche, Dollard des Ormeaux, Quebec H9B 3E5 (CA). THERIEN, Michel [CA/CA]; 944 21st Avenue, Laval, Quebec H7R 2R2 (CA).

(74) Agent: MURPHY, Kevin, P.; Swabey, Ogilvy, Renault, Suite 800, 1001 de Maisonneuve Boulevard West, Montreal, Quebec H3A 3C8 (CA).

(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

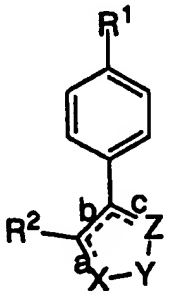
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
13 April 1995 (13.04.95)

(54) Title: PHENYL HETEROCYCLES AS CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of formula (I) useful in the treatment of cyclooxygenase-2 mediated diseases. The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of formula (I).



(I)

INTERNATIONAL SEARCH REPORT

International Application No [redacted] 94/00318

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D277/02 C07D275/02 C07D307/02 C07D333/04 A61K31/33
C07C305/18 C07C307/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 19708 (FUJISAWA PHARMACEUTICAL CO.) 26 December 1991 see examples ---	1-33
E X	WO,A,94 15932 (SEARLE & CO.) 21 July 1994 * see example 13 * ---	1-33 1-22, 24-33
X	* see scheme IV, compound 15, p. 32 ; see example 13, step 4 * ---	23
Y	EP,A,0 087 629 (DU PONT DE NEMOURS) 7 September 1983 see pages 13-14 see page 8; table I --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 1995	07.03.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA94/00318

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]rmation on patent family members

[redacted]ternati[redacted] Application No
[redacted]CT/CA 94/00318

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9119708	26-12-91	AU-A-	7973191	07-01-92
		CN-A-	1059142	04-03-92
		EP-A-	0593761	27-04-94
		JP-T-	6501919	03-03-94
WO-A-9415932	21-07-94	AU-B-	6027694	15-08-94
EP-A-0087629	07-09-83	AU-B-	553269	10-07-86
		AU-A-	1146083	08-09-83
		CA-A-	1242725	04-10-88
		JP-C-	1654086	13-04-92
		JP-B-	3014312	26-02-91
		JP-A-	58159489	21-09-83
		SU-A-	1250172	07-08-86
		US-A-	4590205	20-05-86
		US-A-	4820827	11-04-89
EP-A-0388909	26-09-90	AU-B-	631169	19-11-92
		AU-A-	4768790	12-07-90
		CA-A-	2007133	05-07-90
		EP-A-	0377457	11-07-90
		JP-A-	3014569	23-01-91
		JP-A-	3027370	05-02-91
		US-A-	5145860	08-09-92
		US-A-	5217971	08-06-93
		US-A-	5229386	20-07-93
		CA-A-	2012716	22-09-90